Synthesis and Structure-Activity Studies of Skeletally Modified Estradiol Analogues

by

Pieter David de Koning

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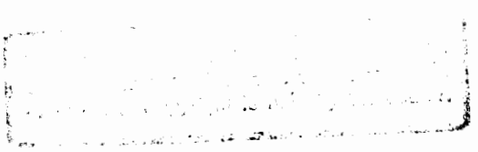
Supervisor: Professor James R. Bull



I declare that '**Synthesis and Structure-Activity Studies of Skeletally Modified Estradiol Analogues**' is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

Signed by candidate

Pieter de Koning

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Summary

In the first phase of this investigation, synthetic approaches to skeletally modified variants of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol were examined, with the purpose of determining the influence of configurational inversion at C-8, C-9 or C-13 upon the high oral estrogenicity associated with introduction of a 14,17-ethano bridge into the estradiol skeleton.

3-Methoxyestra-1,3,5(10)-trien-17-one was converted conventionally into the 13α-isomer, which underwent sequential silyl enol ether formation and dehydrosilylation into 3-methoxy-13α-estra-1,3,5(10),15-tetraen-17-one, which failed to undergo conversion into the corresponding 3-methoxy-13α-estra-1,3,5(10),14,16-pentaen-17-yl acetate required for cycloaddition studies.

Hydrogenation of 3-methoxyestra-1,3,5(10),8,14-pentaen-17β-yl acetate afforded 3-methoxy-8α-estra-1,3,5(10)-trien-17β-yl acetate, which was converted into 3-methoxy-8α-estra-1,3,5(10),14,16-pentaen-17-yl acetate. Cycloaddition with phenyl vinyl sulfone gave a mixture of products, which was converted into the desired 14,17α-ethano-8α-estra-1,3,5(10)-triene-3,17β-diol, by a hydrogenation, desulfonylation, deprotection reaction sequence. The unexpectedly complex result for the cycloaddition reaction was interpreted with the assistance of other cycloaddition reactions of the $\Delta^{14,16}$-dienyl acetate.

17,17-Ethylenedioxy-3-methoxy-9β-estra-1,3,5(10)-trien-11-one was readily prepared from estrone using conventional methodology. Deoxygenation followed by standard functional group manipulation afforded 3-methoxy-9β-estra-1,3,5(10)-trien-17-one. As a result of the poor overall yield, the optimisation of a number of steps in this reaction sequence was investigated. Despite some improvement in the yields, subsequent conversion into the target, 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diol was not synthetically useful. However, dehydrogenation of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol followed by standard functional group modification gave 14,17α-ethanoestra-1,3,5(10),9(11)-tetraene-3,17β-diyl diacetate, hydrogenation of which afforded 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diol, after conventional deprotection, in moderate yield.

Preliminary studies directed towards the synthesis of 15,17-bridged estradiol derivatives are also described. 3-Methoxyestra-1,3,5(10),15-tetraen-17-one was converted into 17α-allyl-15β-phenylthioestra-1,3,5(10)-triene-17β-ol, to allow for generation of a radical at C-15 in order to investigate the scope for cyclisation. An oxy-Cope rearrangement of 17α-allyl-3-methoxyestra-1,3,5(10),15-tetraen-17β-ol afforded 15α-allyl-3-methoxyestra-1,3,5(10)-trien-17-one. Subsequent modification gave 15α-formylethyl-3-methoxyestra-1,3,5(10)-trien-17-one for attempted reductive cyclisation. The feasibility of achieving an intramolecular aldol condensation was examined on the Wacker oxidation product of 15α-allyl-3-methoxyestra-1,3,5(10)-trien-17-one, 15α-acetonyl-3-methoxyestra-1,3,5(10)-trien-17-one. In addition, the synthesis of 15β,17β-bridged compounds was investigated by similar reductive coupling methodology.

A molecular modelling study was undertaken to investigate the structure activity relationships of skeletally modified estradiol analogues, in order to develop a working hypothesis for interpreting and/or predicting their competitive binding affinities towards the estradiol receptor. The structures of three compounds, 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol, 14,17α-propanoestra-1,3,5(10)-triene-3,17β-diol and 14β,17β-propano-14β-estra-1,3,5(10)-triene-3,17β-diol were determined by the molecular mechanics technique of energy minimisation. These conformations were validated by comparison with those observed by X-ray crystallographic determination, and energy minimisation was shown to be a reliable method for determining molecular structures.

The minimum energy conformations of several skeletally modified estradiol analogues were then compared with estradiol by superimposition, in order to identify key regions affecting receptor binding affinity. From this study the steric environment of the ring D region of the receptor has been mapped. Steric bulk on the α-face seems to be readily accommodated without a loss of binding affinity, and in some cases with enhanced affinity. However, steric bulk on the β-face in conjuction with a 17α-hydroxy group significantly reduces the binding affinity. With this working hypothesis, predictions were made regarding the binding affinities of several synthetic targets.

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Chapter 1

Introduction

Historically, the process of drug discovery has consisted of screening large quantities of test materials in biological assays, and, by a process of separation and further screening, identifying the biologically active constituents of the initial sample. Systematic modifications of these initial lead molecules then leads to an understanding of the steric and electronic requirements of the receptor-ligand interaction. With this information, better drugs can then be designed, with greater activity and fewer side-effects. Figure 1.1 summarises the drug discovery process.

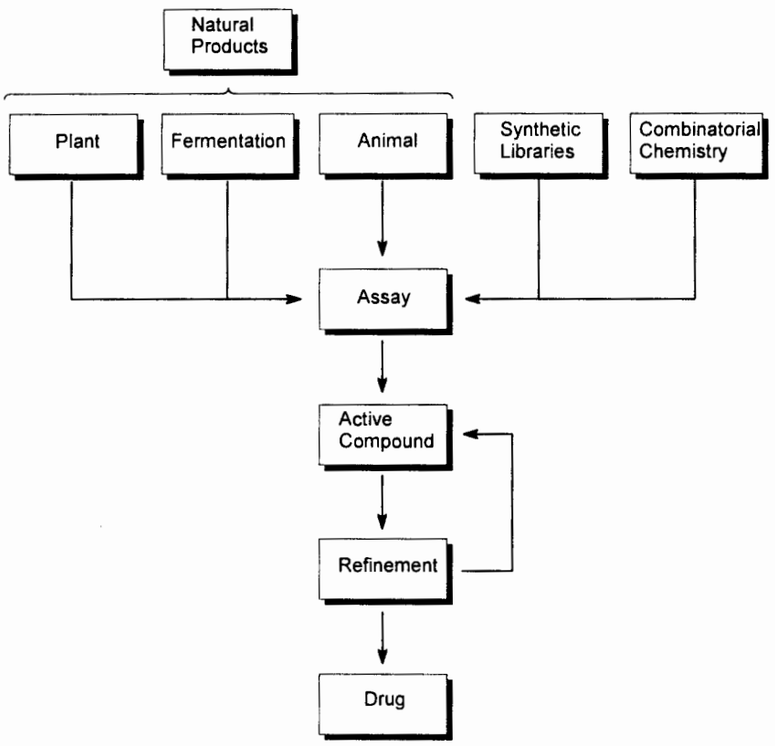


Figure 1.1: Flow-chart summarising the drug discovery process

The cost of developing a new drug is estimated to be over 200 million German marks, requiring the synthesis of 10,000 to 20,000 new compounds (1992 estimate). [1] This enormous expenditure of both time and money, has led to other avenues toward the drug discovery process being explored.

One technique that has been introduced recently is that of combinatorial chemistry [2-5] which enables large numbers of compounds for screening to be synthesised rapidly and economically. At the other end of the drug discovery process, the use of theoretical methods to assist in the drug design process (Figure 1.1, refinement stage) has become an established technique. [1]

These methods vary from computationally intensive quantum-chemical calculations for determining extremely accurate molecular properties [1] to the use of empirical force-fields to obtain information regarding the conformation of molecules, drug-protein interactions and to perform dynamic simulations of drugs. [1] A number of techniques have been developed and applied to establish quantitative relationships between chemical structure and biological activity (quantitative structure-activity relationships, QSAR's). [6-13]

These techniques can assist in the drug discovery process by focusing attention on molecular features that promote and/or retard the biological property of interest. This will enable possible synthetic targets to be ranked according to importance, reducing the burden on overtaxed research programs. It could also assist in directing future experiments by identifying outliers in QSAR correlations. [1]

Although these techniques are capable of providing useful information regarding structure-activity relationships, the results must be regarded with a healthy scepticism, due to the approximate nature of both the theoretical method and the model simulating the biological phenomenon. In addition, the biological tests devised have a different applicability to *in vivo* conditions. It is likely that processes like drug uptake, binding to carrier proteins and properties such as bioavailability are influenced differently by a particular structural modification. [1]

It is known that the characteristic actions of steroid hormones are contingent on the high-affinity binding between the steroid and the specific receptor proteins. In the study of the binding of a ligand to the steroid hormone receptor, a number of different techniques have been identified. [14] The area of interest to this thesis is the study of the steroid-binding site.

This process has thus far been tackled on two fronts: (i) by analysing the amino acid sequences and predicted secondary structures in order to identify possible binding site(s) by computer modelling techniques and (ii) by comparing the 3-D structures and relative binding affinities of steroids in order to deduce the structural features compatible with binding to the receptor and in this way construct an image of the receptor site into which the steroid fits. [14] Another interesting approach currently under investigation is the crystallisation of the receptor protein in order to identify potential binding sites. [15]

In this thesis, the approach of comparing the 3-D structures and relative binding affinities has been investigated for the estradiol receptor. Ultimately, once information regarding the nature of the receptor site has been reliably obtained from either X-ray or NMR investigations, it should be possible to model receptor-ligand interactions and thus obtain structure-activity correlations leading to accurate activity predictions.

Estrogens are substances which are characterised by their ability to produce estrus in females of various mammalian species. The steroidal estrogens are undoubtedly the most important group of these hormones. [16] These hormones were first isolated in the early 1930's in small quantities from the urine of pregnant women and mares. [16] Estradiol (Figure 1.2) was found to be the most active of these natural hormones.

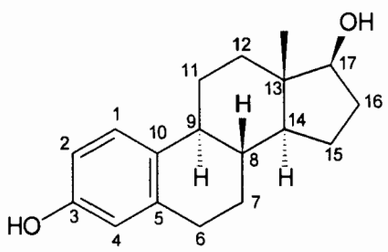


Figure 1.2: Estra-1,3,5(10)-triene-3,17β-diol (estradiol), numbering system indicated

Estrogens play a vital role in a variety of physiological processes within the body, [17, 18] and despite studies linking estrogen use with breast and endometrial cancer remain the only way to prevent post menopausal osteoporosis and to successfully palliate the symptoms of the perimenopause. [19] The effectiveness of estradiol for this purpose suffers from both the

poor oral activity of the drug and its short active lifetime. [20] This has been partially overcome by the use of novel methods of drug delivery, such as patches and gels. [19]

Synthetic estradiol analogues, possessing both greater activity and higher metabolic resistance than estradiol have been the focus of numerous studies. One of the earliest synthetic modifications involved the introduction of a 17α-ethynyl group, giving a synthetic estradiol analogue (ethynylestradiol, Figure 1.3) which is 15-20 times more orally-active than estradiol (Figure 1.2). [21]

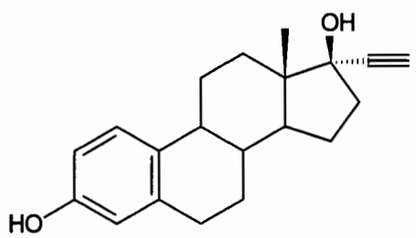


Figure 1.3: 17α-ethynylestra-1,3,5(10)-triene-3,17β-diol (ethynylestradiol)

From systematic variations of functional groups around the periphery of the estradiol skeleton, the mode of receptor-binding, as well as the nature of the receptor have been postulated. In short, the phenolic 3-hydroxy group binds tightly to the receptor through a strong hydrogen bond, subsequently, the 17-hydroxy group interacts with the receptor to induce the biological response. [22, 23] The greater importance of the 3-hydroxy group for binding is evident from the following results: Estra-1,3,5(10)-trien-17β-ol has a competition factor (CF) [24] of 59, [25] substantially inferior to estradiol (CF 1), while estra-1,3,5(10)-trien-3-ol has a CF of 7. [25] The relative orientation of the 17-hydroxy group appears to be critical, as estra-1,3,5(10)-trien-3,17α-diol (the 17-epimer of estradiol) has a CF of 46, once again substantially weaker than estradiol. [25]

An important class of molecules that display affinity towards the estrogen receptor is the non-steroidal stilbene class of compounds, exemplified by diethylstilbestrol (Figure 1.4) which displays high biological activity. [27] For this class of estradiol analogues, which are generally more flexible than steroids, the hydrogen bonding of the phenolic group is thought to be more important than the overall conformation of the molecule in receptor

binding. [22, 26] Although these molecules bear little resemblance to estradiol, they possess the basic structure that appears to be necessary for estrogen receptor affinity, namely (i) a phenolic hydroxyl group and (ii) two hydroxyl groups separated by a hydrophobic spacer.

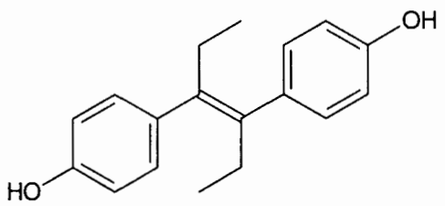


Figure 1.4 : Diethylstilbestrol

The estrogen receptor is generally hydrophobic in nature, as is evidenced by the loss of binding affinity on addition of hydroxy groups to the estradiol template. [26] Apart from a few areas which will be discussed, there appears to be close contact between the ligand and the receptor - the addition of methyl groups in these positions leads to a reduction in biological activity. [26] As has been mentioned, the addition of 17α-substituents does not significantly reduce biological activity, and can even increase it (*cf.* 17α-ethynylestradiol). The 11β- and 7α-positions also appear to be located in the vicinity of a hydrophobic pocket in the receptor, as the introduction of a variety of alkyl and ether groups in these positions enhances biological activity. [26] Recently, it has been established that the introduction of a 14α-methyl group does not impede receptor binding. [28, 29]

It has been estimated that the free energy of binding to the estradiol receptor is in the region of -12.1 kcal mol^{-1} [27, 30] with 3-5 kcal mol^{-1} contributed by the hydrogen bonding of the two hydroxyl groups. [27] This leaves at least 7 kcal mol^{-1} of the binding energy being contributed by hydrophobic interactions between the receptor and the ligand. This should provide sufficient energy to enable a flexible molecule to adopt the most favourable conformation for binding with the receptor. This argument has been proposed as a possible explanation for the high biological activity observed for diethylstilbestrol. [27]

With the discovery that 14,17α-ethanoestra-1,3,5(10)-3,17β-diol (Figure 1.5) is an orally-active estrogen, with biological activity similar or superior to 17α-ethynylestradiol, [31] an extensive investigation into structure-activity relationships of other ring D bridged estradiol

analogues was embarked upon. [32-40] The syntheses of a number of these compounds have been reported elsewhere, [32-35] and will not be discussed in this thesis, but the implications of these modifications towards structure activity relationships will be discussed in Chapter 4.

As a part of this ongoing investigation, the work discussed in this thesis set out to investigate the influence of backbone modifications on the biological activity of estradiol analogues. Skeletally modified hormone analogues are of interest, [41] as it has been shown that they often display promising activity. For example, 9β,10α-progesterone ('retroprogesterone') is approximately 25 times more active than progesterone. [42] As the 14α,17α-ethano bridge is known to enhance biological activity in the natural series, the syntheses of skeletally modified versions of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol (Figure 1.5) were investigated.

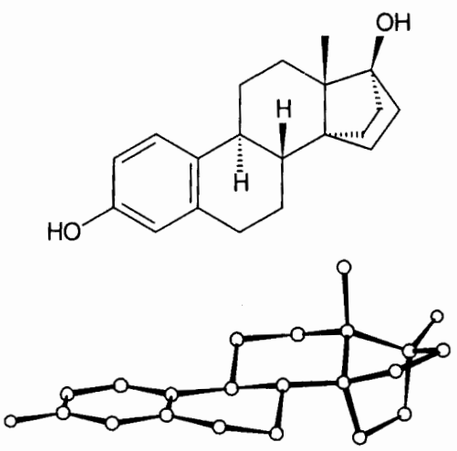


Figure 1.5: 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol **A**

At present, little has been reported regarding the effect of inversion at C-13 on the biological activity of estradiol analogues. [43-46] As can be seen from the perspective drawing of the target (Figure 1.6) ring C is forced to adopt a boat-like conformation. Also evident from this perspective view is that substantial steric bulk is introduced on the β-face of the steroid.

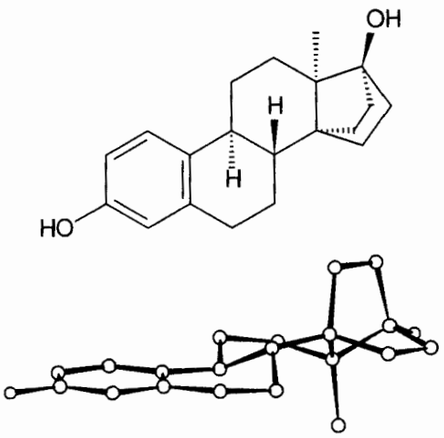


Figure 1.6: 14,17α-ethano-13α-estra-1,3,5(10)-triene-3,17β-diol **B**

Steroids in other series with this modification are known to display interesting pharmacological properties, for example the 13α-gonane derivative ZK 98299 (Figure 1.7), which displays anti-progestational activity. [47]

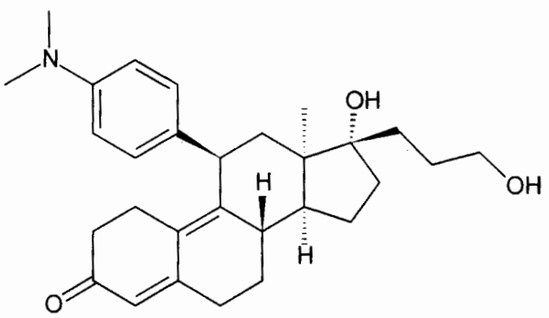


Figure 1.7: The anti-progestational steroid, ZK 98299

Inversion at C-8 results in a dramatic distortion of the planar steroid structure, with rings C and D virtually perpendicular to the plane described by rings A and B (Figure 1.8). Despite this rather drastic change estradiol analogues with this modification retain biological activity, often displaying activities comparable to the natural series. [48-52] For example, 8α-estra-1,3,5(10)-triene-3,17β-diol displays biological activity comparable to estradiol. [48]

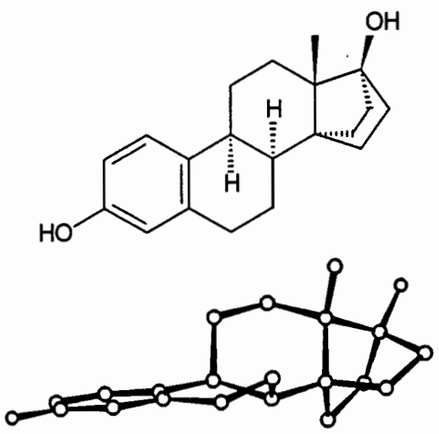


Figure 1.8: 14,17α-ethano-8α-estra-1,3,5(10)-triene-3,17β-diol **C**

Inversion at C-9 results in a steroid with the 'folded' conformation indicated (Figure 1.9). Estratrienes with this configuration are known, and although most display lower biological activity than the corresponding compound in the natural series [53, 54, 28, 29] there are some notable exceptions. The 9β-isomer of 17α-ethynylestradiol is reported to have a binding affinity comparable to the natural series [53] and even more remarkably, 3-hydroxy-9β-estra-1,3,5(10)-trien-11,17-dione has 10 times the estrogenicity of its natural isomer. [54]

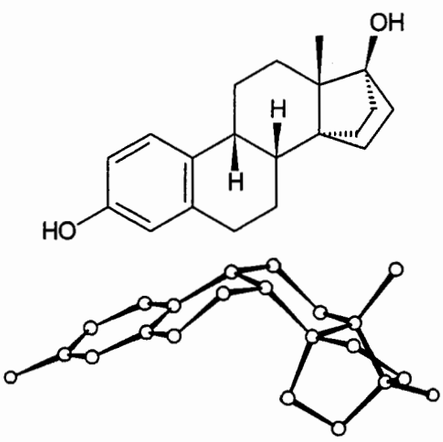


Figure 1.9: 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diol **D**

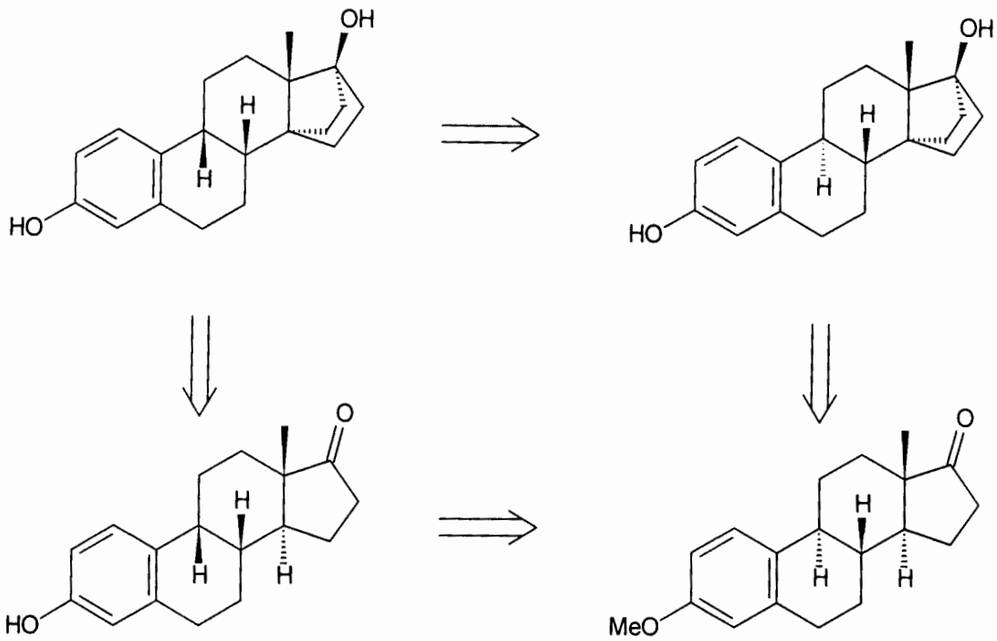
As is evident from the perspective view of the 9β-analogue (Figure 1.9), the structures of 9β-steroids are rather different to that of the parent hormone, notably in the spatial orientation of the two polar functionalities. It has been speculated that these molecules

may undergo conformational deformation during the receptor binding process, thus leading to the observed biological activity. [41]

In an attempt to potentiate steroids towards conformational deformation, Bull *et. al* have synthesised 14α-methyl-9β-steroids, [28, 29, 41] as the introduction of a further sterically impeding group on the already crowded α-face was expected to promote this conformational change. This was partially realised in the estratriene series: 17β-*t*-butyloxy-14α-methyl-9β-estra-1,3,5(10)-trien-3-ol was shown to have a ring B boat, ring C chair conformation, one ring having inverted. [55, 56] The introduction of an 11β-hydroxy group, which further destabilises the ring C chair conformation through a 1,3-diaxial interaction with the 13β-methyl group, sufficed to induce ring C to adopt a non-chair conformation. [55]

Thus, it was anticipated that the 14α,17α-ethano bridge would potentiate the 9β-steroid **D** (Figure 1.9) towards conformational deformation resulting in a (relatively) flexible estradiol analogue. This conformational mobility might predispose the molecule towards an *in vivo* conformational change enabling the most favourable receptor-ligand interaction to occur, leading to higher biological activity.

A retrosynthetic analysis of the target molecules (14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diol is used as an example, Scheme 1.1) indicates two plausible synthetic routes. In the first route, inversion at C-9 affords the known 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol, which is readily available from estrone 3-methyl ether. [57] Alternatively, removal of the 14,17α-ethano bridge affords 3-hydroxy-9β-estra-1,3,5(10)-trien-17-one, which should be available from estrone 3-methyl ether.



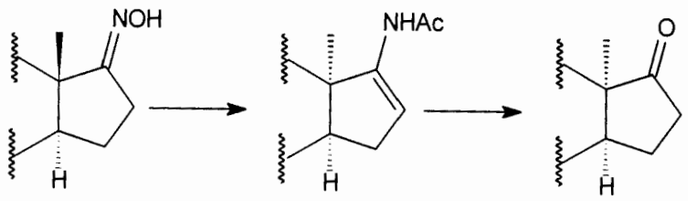
Scheme 1.1 : Retrosynthetic analysis

A more detailed synthetic strategy, based upon this retrosynthetic analysis, followed by the attempted synthesis will be presented for each series in turn. This will be discussed in the next chapter.

Concurrent with this synthetic work, a detailed computational study of these four 14,17α-ethanoestradiol analogues has been conducted, and will be elaborated upon in Chapter 4. In addition, a more general modelling study of ring D bridged estradiol analogues has been carried out in order to deduce the structural features that are compatible with receptor binding, and hence to construct an image of the receptor cavity in which the ligand is bound. This will be discussed in more detail in Chapter 4.

Scheme 2.1

Secondly, heating the oxime of a 17-oxo steroid in a mixture of acetic anhydride and pyridine followed by hydrolysis of the resultant enamide affords the 13α-derivative. [44] (Scheme 2.2)

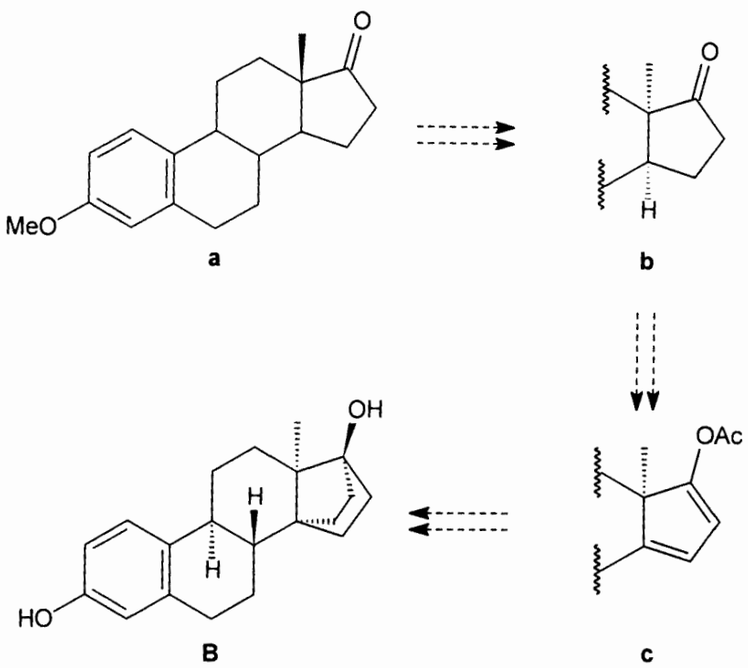


Scheme 2.2

Thirdly, refluxing the 17-oxime acetate (of a 17-oxo steroid) with nickel powder in a mixture of acetic acid and octane affords the 13α-derivative. [45]

As it has been reported that the first two methods are unsuitable for the large-scale preparation of 13α-estrone 3-methyl ether, [58] the third method was selected for introducing the desired unnatural stereocentre.

Two approaches towards the synthesis of the desired ring D bridged 13α-estradiol analogue are conceptually possible, namely introduction of the unnatural stereocentre, followed by the addition of the 14,17-bridge or alternatively, introduction of the 14,17-bridge followed by inversion at the desired stereocentre. In this instance, the latter was not investigated as all the available methods for inversion at C-13 require the presence of a 17-ketone, a functional group which is excluded by the presence of a 14,17-bridge.

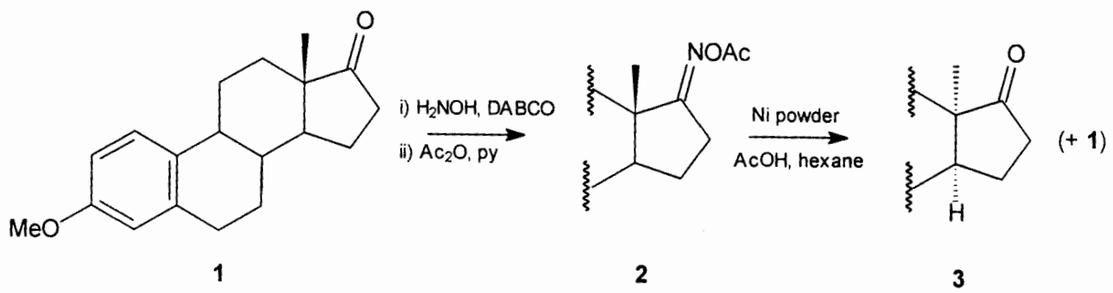


Scheme 2.3: Planned synthetic route

Thus, the planned synthetic route is initial inversion at C-13 of estrone 3-methyl ether **a**, followed by conversion to the derived dienyl acetate **c** for cycloaddition of an ethylene equivalent and subsequent modifications to afford the target **B** (Scheme 2.3).

The crucial step of this synthetic sequence was expected to be the formation of the dienyl acetate **c** as it is readily apparent from simple molecular models that the introduction of a sp^2-hybridised carbon at C-14 of a 13α-steroid forces ring C to adopt a high-energy, boat-like conformation.

Estrone 3-methyl ether **1** was converted into the corresponding 17-oxime acetate **2**,[59, 60] which was treated with nickel powder in refluxing acetic acid-hexane to give a readily separable mixture of 13α-estrone 3-methyl ether **3** (51% from **1**) and estrone 3-methyl ether **1** (8%) (Scheme 2.4). When the reaction was conducted in refluxing acetic acid-octane as described in the literature, [45] a lower yield (44%) of the desired product, along with a comparable amount of estrone 3-methyl ether (7%) was obtained.



1 2 3

Scheme 2.4

The 13α-derivative **3** displayed physical characteristics comparable to the literature values thus confirming the structure. As limited NMR data have been published for compounds with this unusual 13α-configuration, the full assignment of both the proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra was conducted to assist with assignments later in the synthetic sequence. Standard spectroscopic techniques, for example ^{1}H-^{1}H correlation spectroscopy (COSY) and ^{13}C-^{1}H correlation spectroscopy (HETCOR) were used to assist with these assignments.

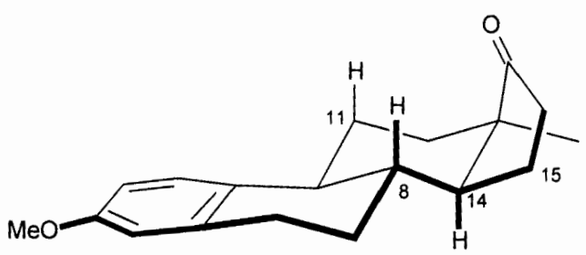


Figure 2.1: Perspective drawing of 13α 17-ketone **3**

Some interesting features were observed in the ^{1}H NMR spectrum; the signal for 14α-H appeared as a doublet of doublets (δ 1.75, *J* 11 and 6 Hz) in which the large coupling is to 8β-H and the small coupling to 15α-H. No coupling with 15β-H is observed, owing to a near-orthogonal relationship between 14α-H and 15β-H [61] clearly evident from an examination of a model. The signals for 8β-H (δ 0.92) and 11β-H (1.0) are both in the region of anisotropic shielding of the 17-ketone, [62] clearly indicated from a comparison with the comparable shifts for estrone 3-methyl ether: 8β-H (δ 1.2) and 11β-H (δ 1.3), [63]

confirming the molecular conformation indicated (Figure 2.1). Figure 2.2 shows the high-field region of this spectrum.

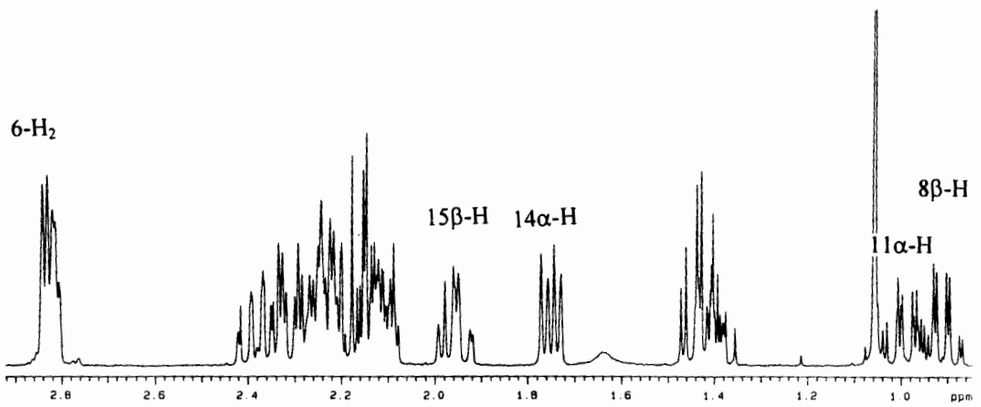
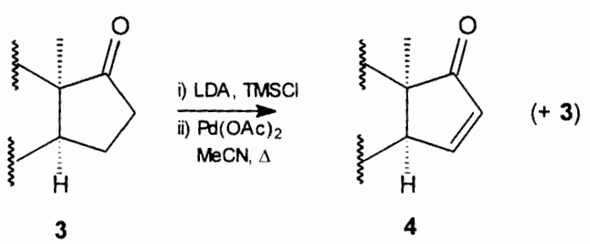


Figure 2.2: ^{1}H NMR spectrum of 13α 17-ketone **3**

The introduction of unsaturation into ring D was performed according to a standard procedure [64] which has been used successfully in the dehydrogenation of steroidal 17-ketones. Thus, the 17-ketone **3** was converted *via* a low-temperature deprotonation-trapping sequence (LDA, TMSCl) into the corresponding silyl enol ether which was treated directly with palladium acetate in refluxing acetonitrile to give a separable mixture of starting material **3** (33%) and the desired Δ^{15} 17-ketone **4** (38%) (Scheme 2.5). This rather poor result contrasts with those reported [65, 66] for 17-oxosteroids in the natural series, and may be ascribed to greater steric hindrance towards palladium complexation to the olefinic bond in the enol silyl ether. The 13α-methyl group thus inhibits α-face complexation, whereas the β-face is subjected to severe steric hindrance by the elements of ring C, with the result that competing hydrolysis under the acidic reaction conditions becomes significant.



3 **4**

Scheme 2.5

The Δ^{15} 17-ketone **4** was readily characterised by spectroscopic techniques - an infrared absorption (ν_{max} 1701 cm^{-1}) clearly indicated the presence of a cyclopentenone sub-unit. AB Multiplets for 15-H (δ 7.76, dd *J* 5.8 and 2.6 Hz) and 16-H (δ 6.18, dd *J* 5.8 and 1.7 Hz) were observed confirming the presence of the conjugated olefinic bond. The signal for 14α-H (δ 2.7, ddd *J* 11.6, 2.6 and 1.7 Hz) displayed the expected coupling pattern and enabled identification of most of the ^{1}H NMR spectrum, and the ^{13}C NMR spectrum with the aid of 2D correlation spectroscopy.

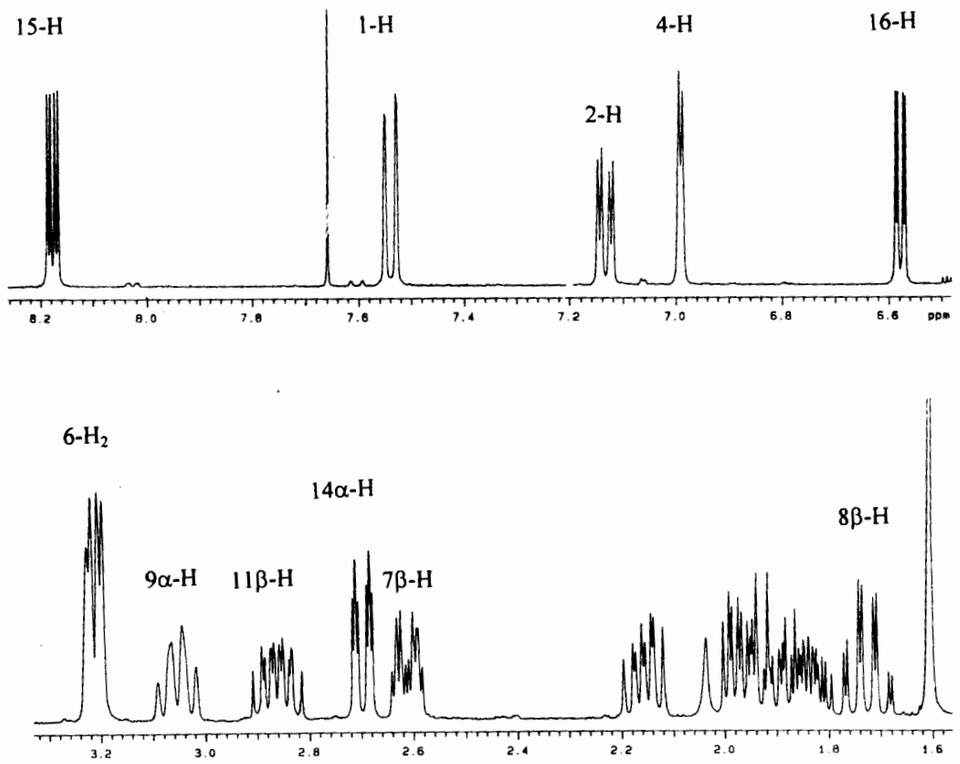


Figure 2.3: ^{1}H NMR spectrum of Δ^{15} 17-ketone **4**

Conversion of the Δ^{15} 17-ketone **4** into a 14,16-dienyl derivative for cycloaddition studies was expected to be problematical. Examination of molecular models clearly indicates that the change of hybridisation at C-14 from sp^3 to sp^2 forces ring C to adopt a boat-like conformation (Figure 2.4). This was expected to increase the activation energy of the reaction and possibly prevent it from occurring altogether.

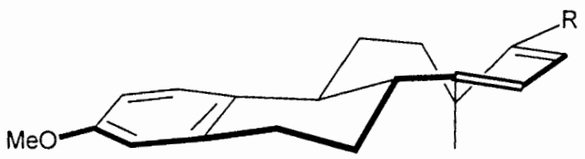
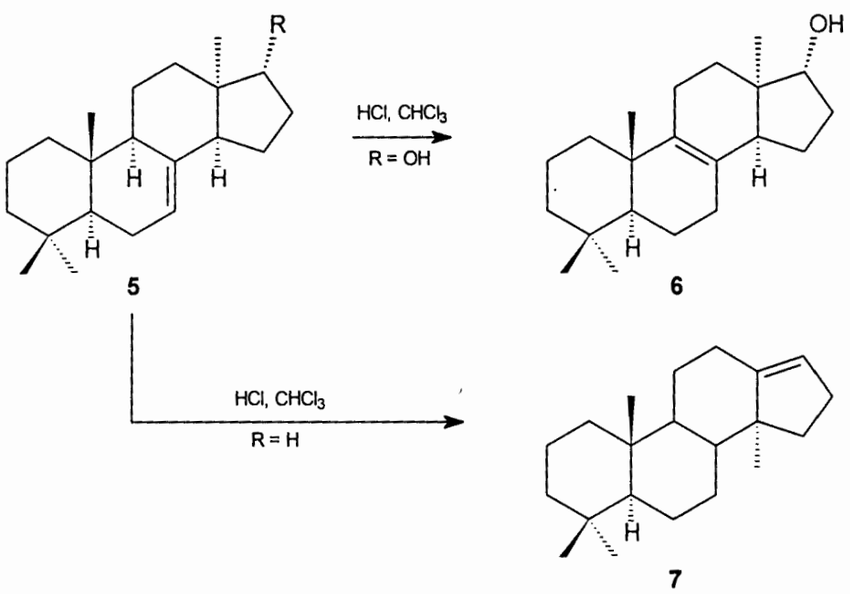


Figure 2.4: Perspective view of the desired 14,16-dienyl system

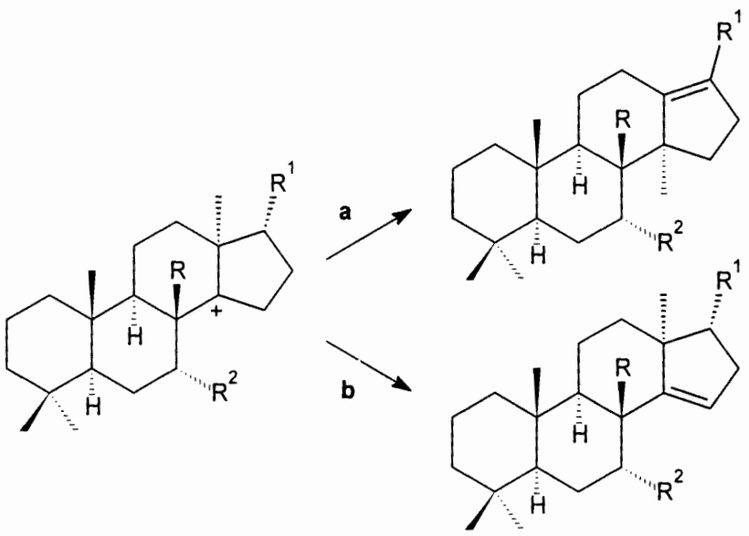
A review of the literature was undertaken to establish whether or not this structural sub-class (13α-Δ^{14} system) has been described, as these compounds would be expected to have ring C in a boat-like conformation.



Scheme 2.6

A reported attempt to introduce a Δ^{14}-bond into a 13α-methyl steroid by the acid catalysed isomerisation of an olefinic bond [67] (HCl, $CHCl_3$) indicated that, in contrast with the natural series, the Δ^{7}-olefin **5** either isomerises to the Δ^{8}-isomer **6** (R = OH) or to the $\Delta^{14(17)}$-14α-methyl derivative **7** (R = H), with none of the desired Δ^{14} 13α-methyl derivative being formed (Scheme 2.6). The introduction of a Δ^{14}-bond has been successfully accomplished in related 13α-steroids with a 7α-substituent [68] so this result was somewhat unexpected.

The authors proposed the following explanation (Scheme 2.7): the collapse of a carbocation (incipient or otherwise) at C-14, either by the migration of the 13α-methyl group (pathway **a**) or by the elimination of a 15-proton (pathway **b**) is determined by the 7α-substituent (R^2). Where this substituent is small (e.g. H) pathway **a** is favoured. However, the presence of a bulkier 7α-substituent (e.g. OH) leads to a 1,3-diaxial interaction in the transition state as the 13α-methyl group migrates to C-14 so that pathway **b** becomes competitive. [67]

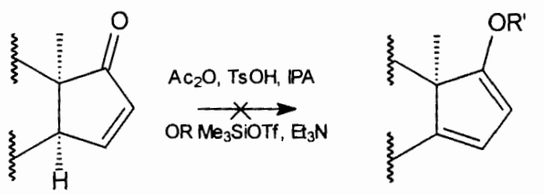


Scheme 2.7

Despite this negative precedent, it was decided to proceed with attempts to synthesise the 14,16-dienyl system in the hope that the additional stabilisation provided by conjugation would stabilise the system sufficiently to enable isolation of the diene and subsequent cycloaddition reactions to proceed smoothly.

The first method to be investigated for accomplishing this transformation was that successfully utilised in the synthesis of 3-methoxyestra-1,3,5(10),14,16-pentaen-17β-yl acetate. [57] Refluxing the Δ^{15} 17-ketone **4** with toluene-*p*-sulfonic acid in a mixture of acetic anhydride and isopropenyl acetate (IPA) afforded a less polar product in poor yield (9%) which displayed ^{1}H NMR features consistent with the desired dienyl acetate **8** (Scheme 2.8), namely two low field signals for 15-H (δ 5.85, m) and 16-H (δ 6.17, d, *J* 2.3

Hz), and an acetate methyl signal (δ 2.23, s) for the 17-OAc. The expected molecular ion (*m/z* 324) was also observed in the mass spectrum. Further characterisation was rendered difficult due to the instability of the material, and in the light of the previous discussion the limited data set does not provide conclusive structural proof. As a result of the poor conversion, the uncertainty regarding the outcome and the instability of the product this reaction was not examined further.



4 **8** R' = Ac
9 R' = $SiMe_3$

Scheme 2.8

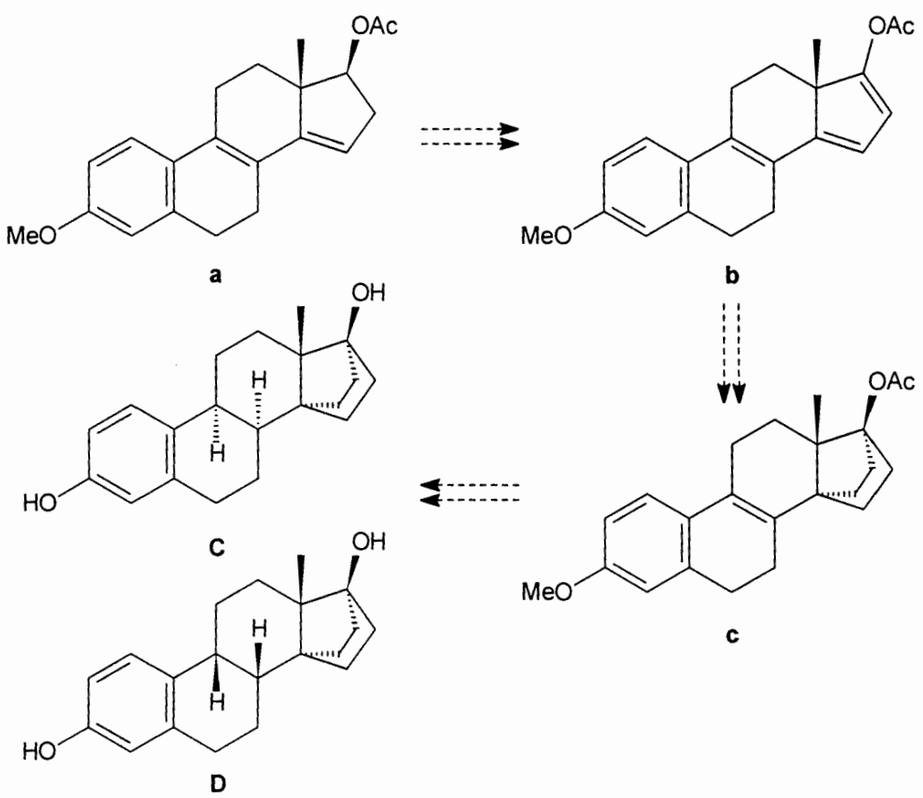
As an alternative route towards the $\Delta^{14,16}$-dienyl system, the synthesis of the derived $\Delta^{14,16}$ 17-silyl dienol ether **9** was explored. Treatment of the Δ^{15} 17-ketone **4** with trimethylsilyl trifluoromethanesulfonate and triethylamine (TEA) in dichloromethane gave a single, less polar, UV active fraction (27%) which ^{1}H NMR analysis indicated to be a mixture of products, possibly containing the desired product **9**, but the instability of this mixture prevented any further investigation.

The formation of the more stable triisopropylsilyl dienol ether using similar reaction conditions (triisopropylsilyl trifluoromethanesulfonate, TEA) was also attempted with similar results.

These preliminary experiments confirmed that formation and cycloaddition of 14,16-dien-17-yl derivatives in the 13α-series would be difficult, and it was decided that further work on the problem was beyond the scope of this investigation.

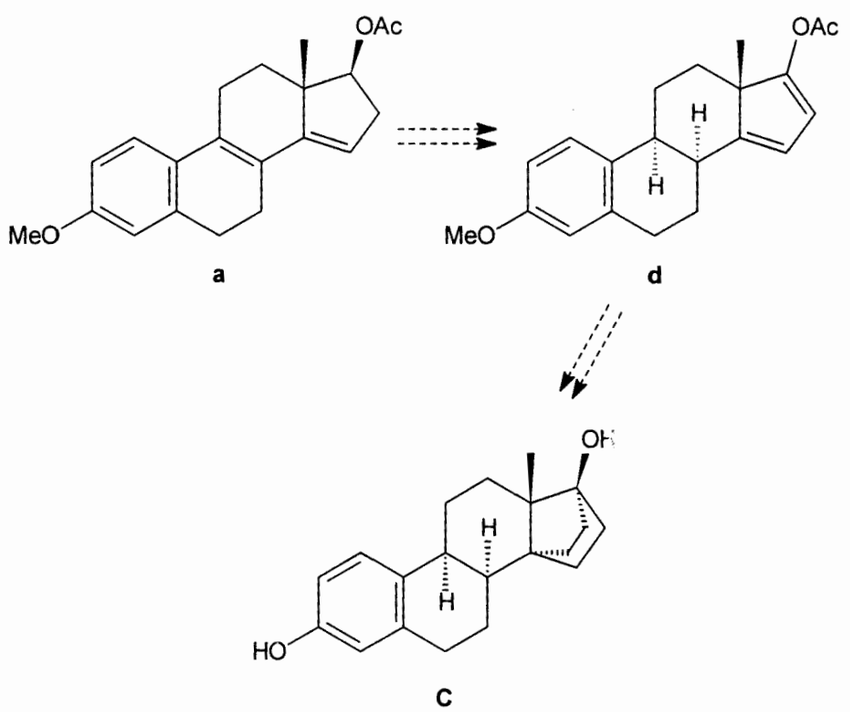
2.2: 8α-Series

The availability of 3-methoxyestra-1,3,5(10),8,14-pentaen-17β-yl acetate **a** [69] as starting material suggested two possible approaches to the target system, 14,17α-ethano-8α-estra-1,3,5(10)-triene-3,17β-diol **C**. In the first approach (Scheme 2.9), conversion of 17β-acetate **a** into the corresponding hexaenyl derivative **b** would provide an intermediate for cycloaddition of an ethylene equivalent to the ring D moiety. It was reasoned that the presence of the 14α,17α-ethano bridge in **c** would diminish the α-selectivity associated with the catalytic hydrogenation of the Δ^8-bond in the unbridged series. [48] Thus, catalytic hydrogenation of the olefinic bond in the bridged compound **c** was expected to furnish the desired 14,17α-ethano-8α-estra-1,3,5(10)-triene-3,17β-diol **C**, almost certainly accompanied by the corresponding 9β-isomer **D**. Such an outcome would, in fact, be advantageous since generation of both isomers in practical yields would thus provide access to two of the identified target analogues of estradiol of this investigation.



Scheme 2.9

The alternative strategy (Scheme 2.10) was to subject the pentaene **a** to catalytic hydrogenation and to convert the resultant 8α-derivative, [48] into the derived dienyl acetate **d** for cycloaddition of an ethylene equivalent and subsequent modification into the target system **C** using the familiar methodology described for the natural series. [57]

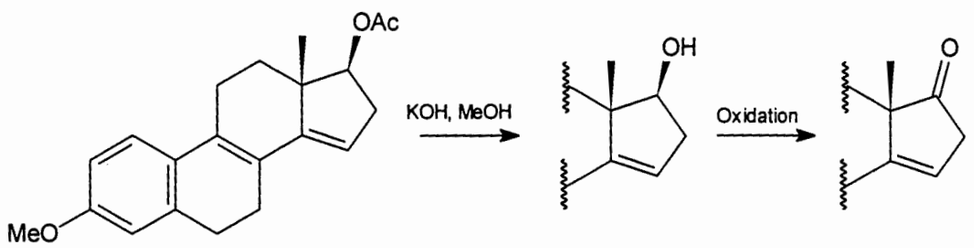


Scheme 2.10

The findings of this investigation into these two synthetic strategies are described in the ensuing section.

2.2.1 Synthesis of 14,17α-ethano-8α-estra-1,3,5(10)-triene-3,17β-diol

Starting from the 17β-acetate **10**, [69] hydrolysis of the ester afforded the 17β-alcohol **11** (Scheme 2.11). [69] Oxidation of this alcohol to the derived 17-ketone **12** proved problematical. A wide variety of oxidation methods [70-76] gave complex mixtures of highly coloured compounds, from which no 17-ketone **12** could be isolated. The use of tetra-*n*-propylammonium perruthenate and N-methylmorpholine N-oxide [77] gave a 20% yield of the 17-ketone **12**, which was still contaminated with coloured material.



10 **11** **12**

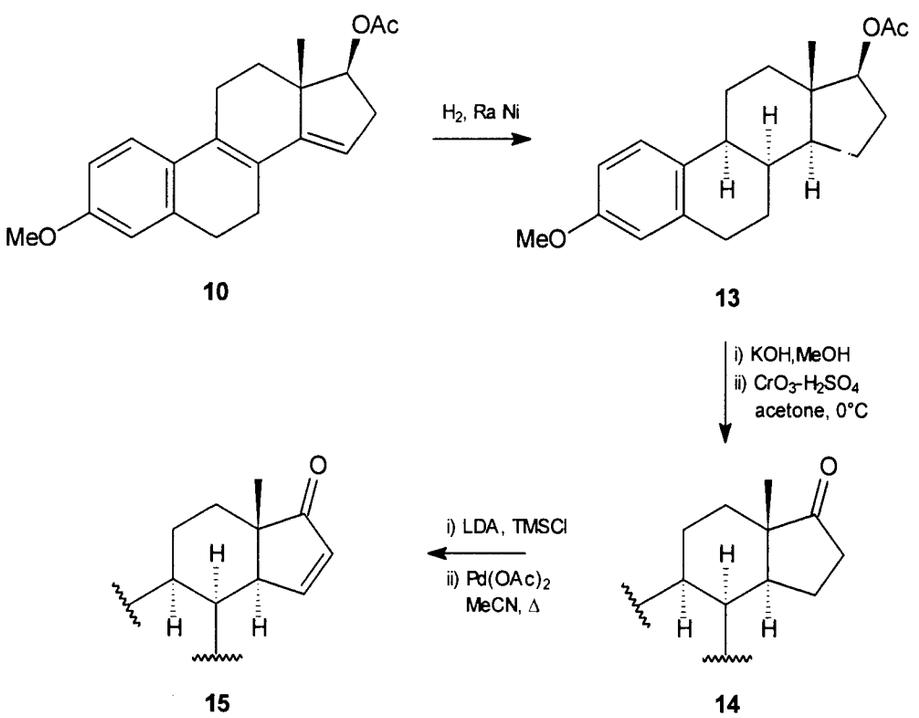
Scheme 2.11

A review of the literature revealed that 3-methoxyestra-1,3,5(10),8,14-pentaen-17-one **12**, has been synthesised by a number of different synthetic routes, mostly in racemic form. [78-82] In one of these reported syntheses, a (racemic) mixture of the 3-methoxyestra-1,3,5(10),8,14-pentaen-17ξ-ols was oxidised to the 17-ketone (*rac.* **12**) with chromium trioxide and Celite in a mixture of dichloromethane and diethyl ether. [82] Utilising these reaction conditions on the optically pure 17β-alcohol **11** was unsuccessful, with no reaction being observed (TLC). As yet, no explanation has been found to account for the problems observed with this oxidation reaction. Due to this problematical reaction this route was discontinued.

The alternative synthetic route (Scheme 2.10) was then investigated. Starting from the 17β-acetoxypentaene **10**, catalytic hydrogenation afforded the 8α-estratriene **13**. The structure of this compound was confirmed by a comparison of physical characteristics (m.p. and $[\alpha]_D$) with literature values. [48] Raney nickel was used as the catalyst for this

reaction as it has been reported [48] that palladium catalysis affords side products, resulting from dehydrogenation of ring B.

Hydrolysis of the 17β-acetate **13**, followed by oxidation with Jones' reagent [83] (other oxidants worked equally well) gave the desired 17-ketone **14** in 87% overall yield from **10**. Conclusive ^{1}H NMR evidence for the 8α-configuration could not be obtained, as the signals for 8α-, 9α- and 14α-H were all overlapped with other signals, nevertheless the observed physical characteristics (m.p. and $[\alpha]_D$) compared well with literature values. [48]



10 **13** **15** **14**

Scheme 2.12

In order to help with assignments later in the series, the ^{1}H NMR spectrum of **14** was assigned as fully as possible. Figure 2.5 shows the high-field region of this spectrum.

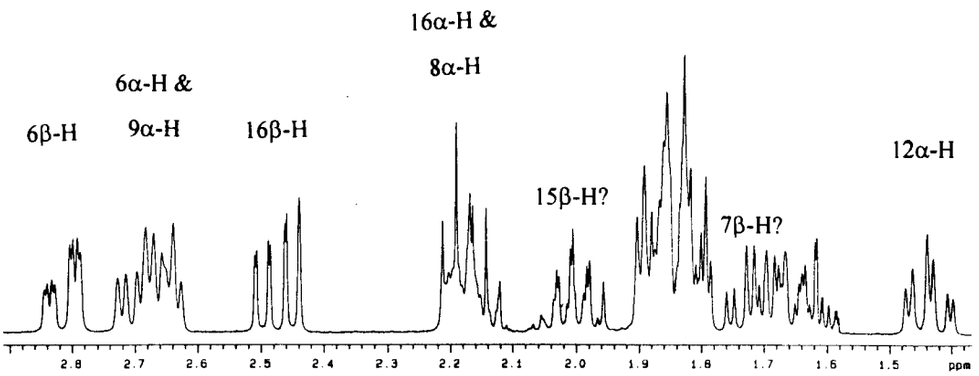


Figure 2.5: High-field region of the ^{1}H NMR spectrum of 8α 17-ketone **14**

Introduction of unsaturation into ring D was accomplished by the enol silylation-dehydrosilylation procedure [64] previously described for the 13α-series. A low temperature deprotonation-trapping sequence (LDA, TMSCl) afforded the corresponding enol silyl ether which was treated with palladium acetate in refluxing acetonitrile to give a quantitative yield of the Δ^{15} 17-ketone **15** (Scheme 2.12). All the spectral and analytical evidence clearly indicated that the expected conversion had occurred, namely an infrared absorption consistent with a cyclopentenone (ν_{max} 1707 cm^{-1}) and the expected AB multiplets for both 15-H (δ 7.59, ddd, *J* 6.0, 2.0 and 0.6 Hz) and 16-H (δ 6.09, dd, *J* 6.0 and 3.4 Hz). Figure 2.6 shows the ^{1}H NMR spectrum of **15**.

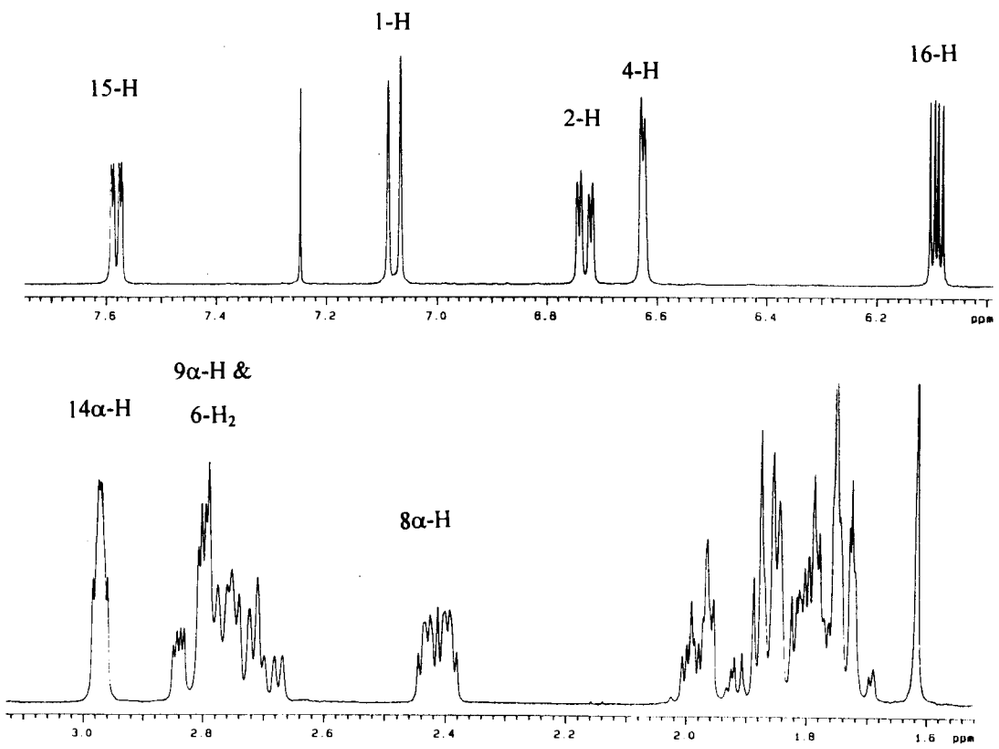
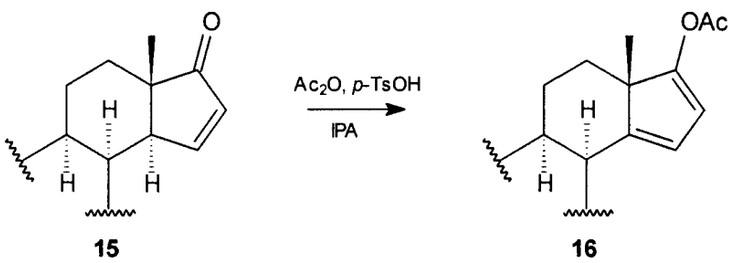


Figure 2.6: ^{1}H NMR spectrum of Δ^{15} 17-ketone **15**.

From the observed signals for 8α-H (δ 2.4) and 14α-H (δ 2.9) the configuration at C-8 could be readily assigned. The signal for 8α-H is a broadened doublet of quartets, with three small couplings (to 7α-H, 9α-H and 14α-H) and one large coupling (to 7β-H). In the case of 14α-H, a signal approximating a quartet is observed, indicating three small couplings (to 8α-H, 15-H and 16-H). The identity of the long-range coupling partner to 15-H could not be determined, even with the assistance of a COSY spectrum.

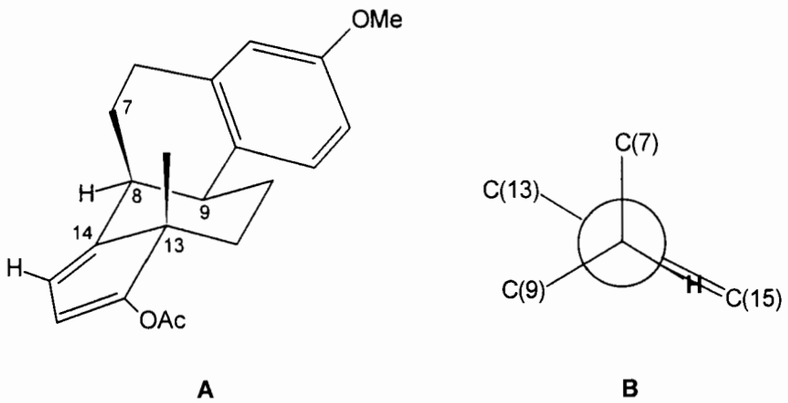
The Δ^{15} 17-ketone **15** was converted to the dienyl acetate **16** following a standard procedure which has been used successfully in the natural series. [57] Refluxing the Δ^{15} 17-ketone **15** in a mixture of acetic anhydride and IPA with catalytic toluene-*p*-sulfonic acid for 2h gave the desired dienyl acetate **16** (78%) (Scheme 2.13).



15 **16**

Scheme 2.13

All the spectroscopic and analytical evidence support the assigned structure [ν_{max} 1748 cm^{-1}, M^+ 324, a methyl signal at δ 2.2 for 17β-OAc, and an AB multiplet for 15-H (δ 5.98, d, *J* 3 Hz) and 16-H (δ 6.08, d, *J* 3 Hz)]. In this case, the signal for 8α-H (δ 2.94, ddd, *J* 13.3, 5.4 and 2.6 Hz) provided further spectroscopic evidence for the configuration at this centre. The lack of an allylic coupling from 15-H to 8α-H [84] is due to the fact that 8α-H is virtually in the plane of the olefinic bond (Figure 2.7), unlike in the natural series, where such a coupling is observed. [57]

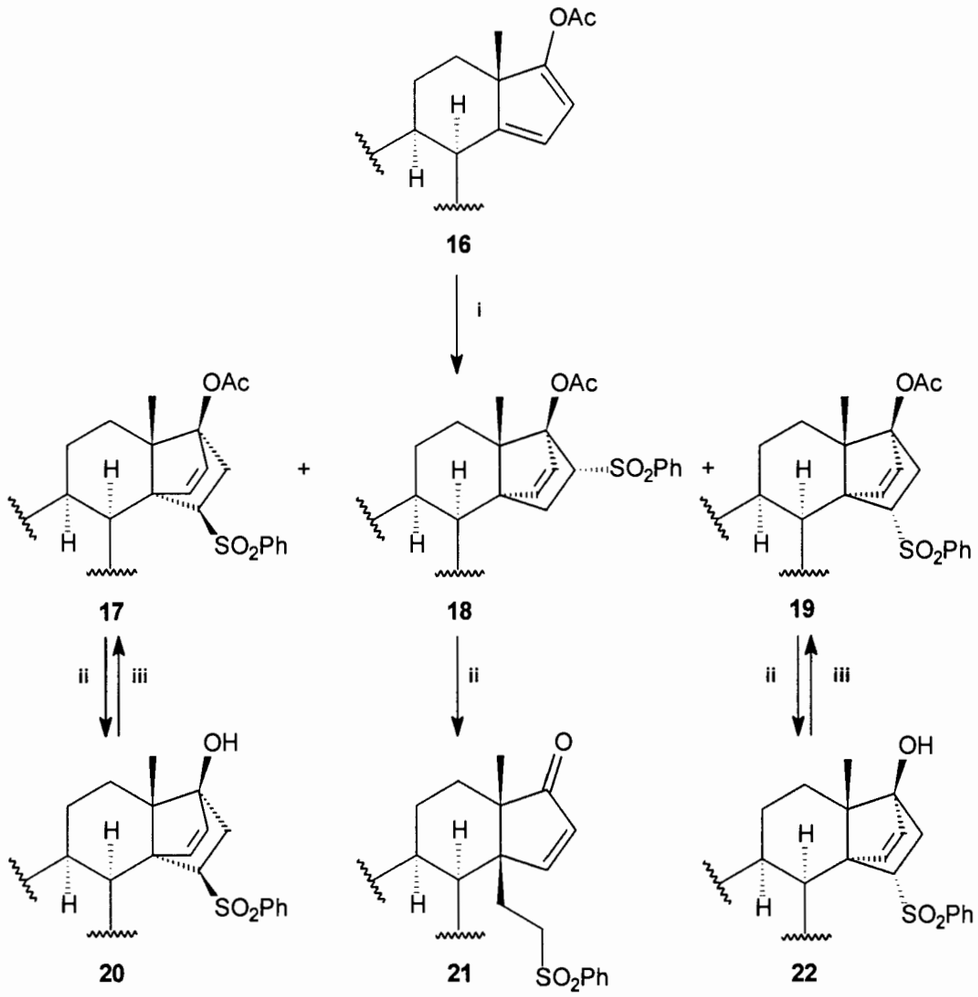


A **B**

Figure 2.7: A, Perspective view of dienyl acetate **16** and **B**, Newman projection along the 8,14-bond

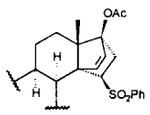
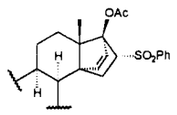
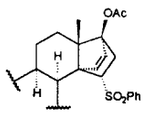
Having successfully synthesised this key intermediate, the introduction of the 14α,17α-ethano bridge was investigated.

Cycloaddition of the dienyl acetate **16** with phenyl vinyl sulfone (PVS) (benzene, 150°C) proceeded slowly (140h) to give what appeared on TLC to be a single product, but was discovered to be a mixture of three cycloadducts **17**, **18** and **19**, approximately in a 1:1:3 ratio (Scheme 2.14). The isolation and characterisation of each adduct will be described separately, however for comparison purposes, important ^{1}H NMR signals of all three adducts have been tabulated (Table 2.1).



Scheme 2.14 *Reagents and conditions*: **i**, $H_2C{=}CHSO_2Ph$, PhH, 150°C; **ii**, KOH, MeOH, 25°C; **iii**, Ac_2O, C_5H_5N, DMAP

Table 2.1: ^{1}H NMR signals for the cycloadducts **17**, **18** and **19**.

	Chemical shift δ/ppm (multiplicity, coupling constant *J*/Hz)		
Proton(s)	 **17**	 **18**	 **19**
15	δ 6.33 (d, *J* 6)	α: δ 1.72 (dd, *J* 12.6 and 4.6) β: δ 2.52 (dd, *J* 12.6 and 9.0)	β: δ 4.03 (dd, *J* 9.0 and 4.8)
16	δ 6.40 (d, *J* 6)	β: δ 4.05 (dd, *J* 9.0 and 4.6)	β: δ 2.09 (dd, *J* 12.3 and 9.0) α: δ 2.63 (dd, *J* 12.3 and 4.8)
17[1]	*exo*: δ 2.14 (dd, *J* 12.2 and 9.4) *endo*: δ 2.57 (dd, *J* 12.2 and 4.3)	δ 6.43 (d, *J* 6)	δ 6.37 (d, *J* 6)
17[2]	*exo*: δ 4.25 (dd, *J* 9.4 and 4.3)	δ 5.96 (d, *J* 6)	δ 6.00 (d, *J* 6)

Chromatography failed to achieve separation and gave a single fraction (79%) comprising a mixture of **17**, **18** and **19**, crystallisation of which gave a single product, **17** (a minor product). From the ^{1}H NMR spectrum, the regio- and stereochemistry of the cycloaddition was not obvious; the expected doublets for the etheno bridge (δ 6.33 and 6.40, *J* 6 Hz), the doublet of doublets for the proton α- to the phenylsulfonyl group (δ 4.25, *J* 9.4 and 4.3 Hz) and the corresponding coupling partners (δ 2.14, dd, *J* 12.2 and 9.4 Hz and δ 2.57, dd, *J* 12.2 and 4.3 Hz) were all clearly visible, but did not exclude any of the possible cycloadducts. Figure 2.8 shows the high-field region of the ^{1}H NMR spectrum of **17**.

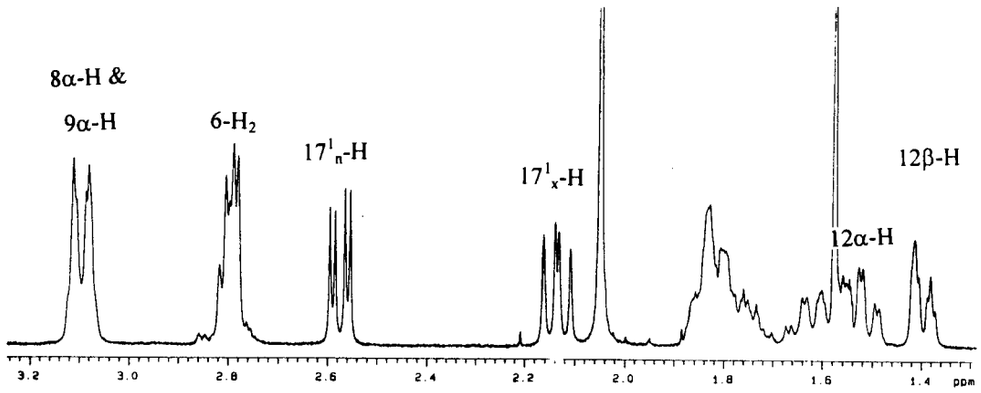


Figure 2.8: High-field region of ^{1}H NMR spectrum of 17^2*R*-phenylsulfonyl 17-acetate **17**

Preliminary structural assignment was made by NOE difference spectroscopy. Irradiation of the 13β-methyl group (δ 1.03) enhanced both olefinic protons (δ 6.33 and 6.40), indicating that an α-face cycloaddition had occurred.

From a NOESY spectrum (a portion of this is shown in Figure 2.10), the structure was readily assigned as that of the cycloadduct **17**. The key signals used in making this assignment were the observed crosspeaks between 17^2-H$_x$ and 8α-/9α-H as well as the crosspeaks between the 13β-Me and C-15 and C-16 (Figure 2.9).

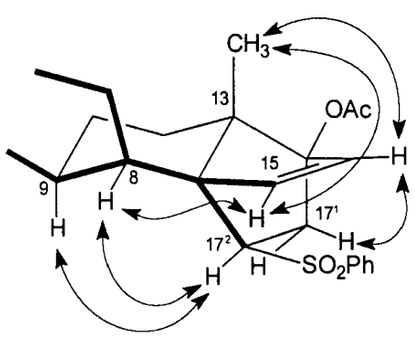


Figure 2.9: Perspective view of17^2*R*-phenylsulfonyl 17-acetate **17** indicating some of the observed NOESY crosspeaks

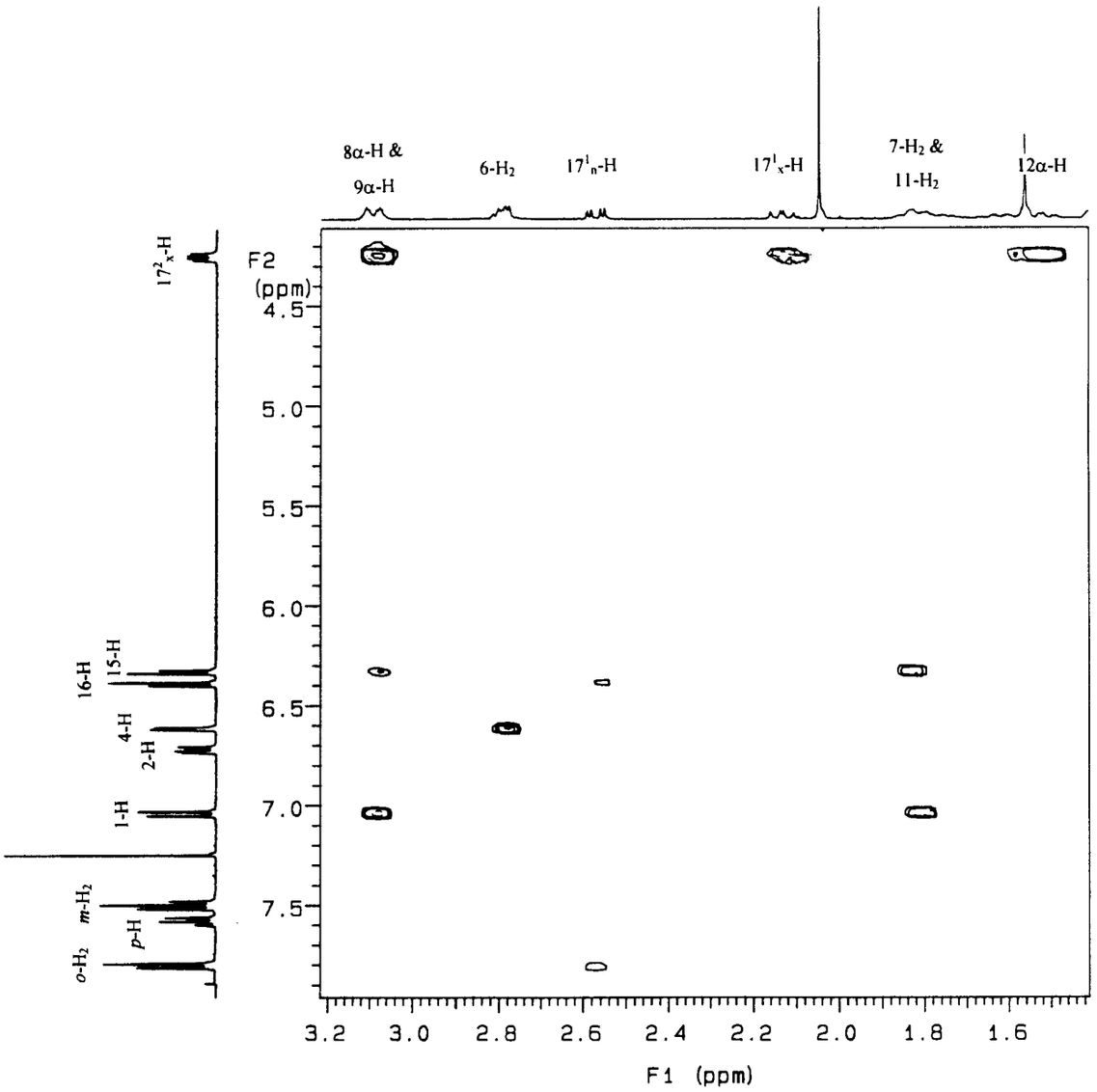


Figure 2.10: NOESY spectrum of 17^2*R*-phenylsulfonyl 17-acetate **17**

As this was a somewhat unexpected result in the light of the extremely selective cycloaddition reactions to the corresponding ring D dienyl acetate with the natural configuration at C-8, [32, 33, 57] an X-ray crystal structure of the cycloadduct **17** was obtained (see Chapter 6 for details), and this provided conclusive proof of the structure (Figure 2.11). This confirmation of the structure allowed further structural assignments from NOE spectroscopy to be made with confidence.

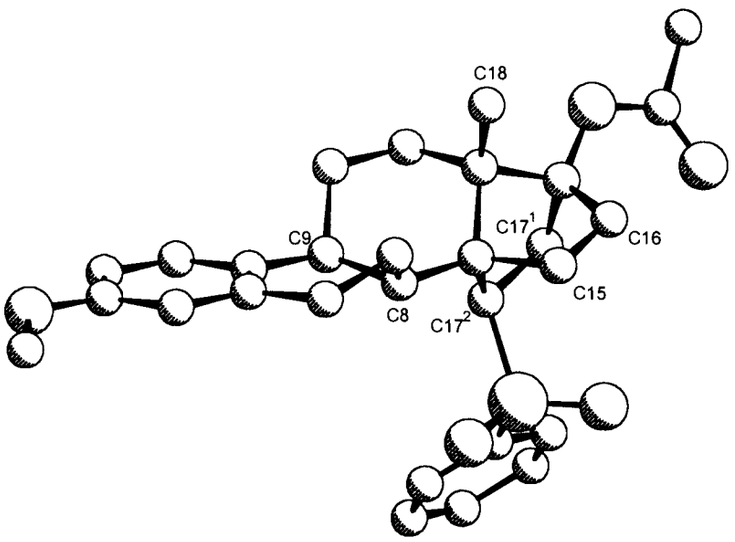


Figure 2.11: X-ray crystal structure of17^2*R*-phenylsulfonyl 17-acetate **17**, important carbons are numbered

Alkaline treatment of the cycloaddition mixture **17**, **18** and **19** gave two fractions, one of which was a single product, less polar than the starting material which absorbed UV light (17%). This was assigned as the 14β-(phenylsulfonylethyl) Δ^{15} 17-one **21**, which must originate from retrograde cleavage (of the 16,17-bond) of adduct, **18**. Both the ^{1}H NMR and IR spectra indicated the presence of a cyclopentenone unit [ν_{max} 1708 cm^{-1}, doublet for 16-H (δ 6.20, *J* 5.9 Hz) and a multiplet for 15-H (*ca* 7.7 - overlapping with other signals)]. Although the available data did not provide conclusive proof of the stereochemistry at C-14, this was confirmed by the subsequent isolation of **18** from the cycloaddition mixture (Scheme 2.15).

The more polar material, an inseparable mixture of **20** and **22**, must originate from hydrolysis of the 17β-OAc of a head-to-tail adduct (Figure 2.14; **17** and **19**). A comparison of the ^{1}H NMR spectrum of this mixture with material prepared by alkaline hydrolysis of pure 17^2-phenylsulfonyl Δ^{15} adduct **17**, (product **20**) clearly indicates that a mixture of two products is indeed present (3:1 ratio by ^{1}H NMR), with the minor isomer corresponding to product **20**.

Reacetylation of this mixture gave a mixture of the two 17β-acetates **17** and **19** which were inseparable on silica gel chromatography. Crystallisation from chloroform-methanol afforded the previously identified 17^2-phenylsulfonyl Δ^{15} adduct **17**, and evaporation of the mother liquor afforded the other head-to-tail adduct, 15α-phenylsulfonyl-14,17α-etheno derivative **19**.

As in the case of **17**, the ^{1}H NMR spectrum displayed the expected signals for a cycloadduct (Table 2.1). Figure 2.12 shows the high-field region of the ^{1}H NMR spectrum.

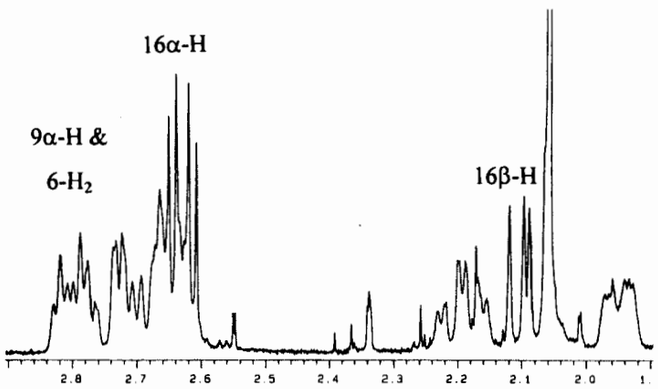


Figure 2.12: ^{1}H NMR spectrum of 15α-phenylsulfonyl 17-acetate **19**

The orientation of the 15-phenylsulfonyl group was expected to be α, but in order to confirm this, a difference NOE experiment was conducted. Irradiation of the 13β-methyl group enhanced the signal for 15β-H (δ 4.03, 4.8%) amongst others, thus providing conclusive structural proof.

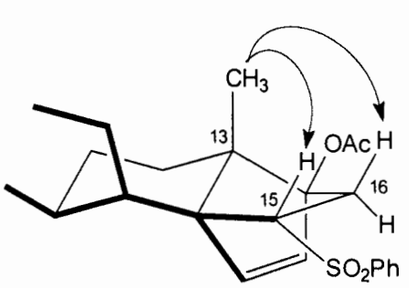
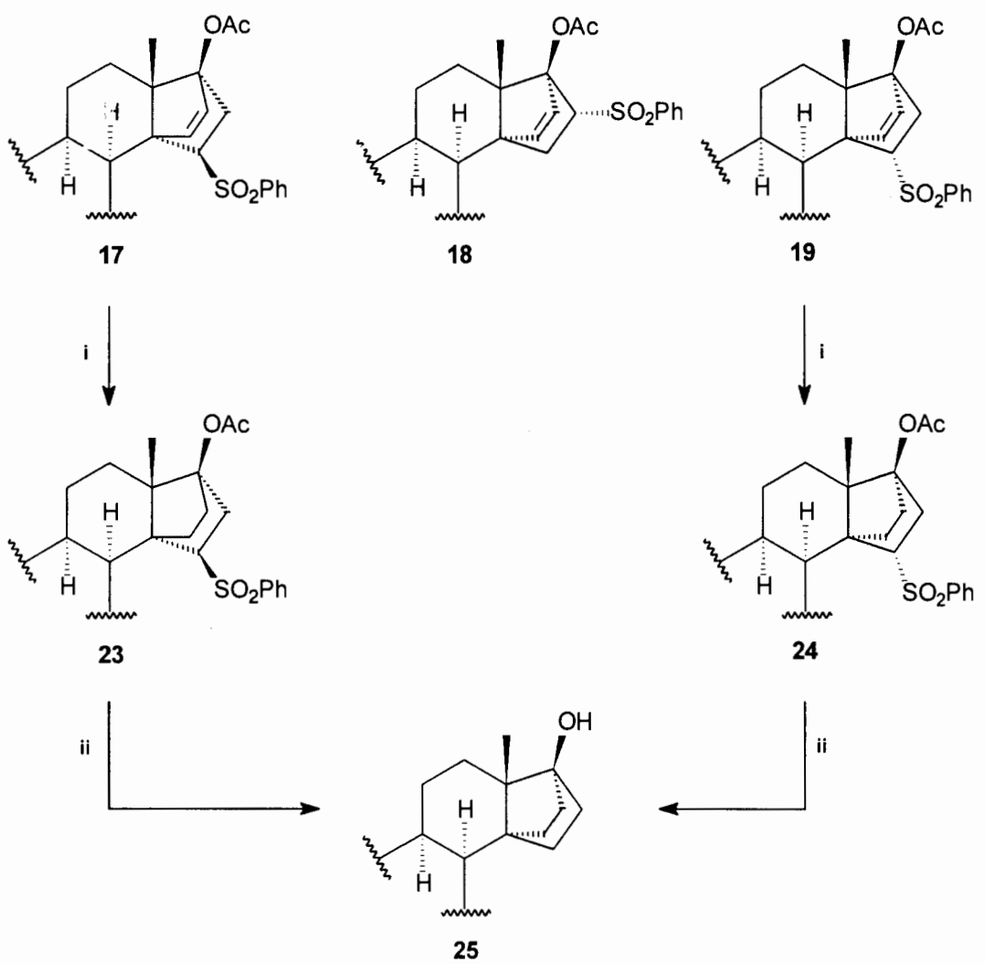


Figure 2.13: Perspective view of 15α-phenylsulfonyl 17-acetate **19** indicating observed NOE enhancements

The total cycloaddition fraction **17**, **18** and **19** was then hydrogenated as the next step towards the target compound. The reaction was performed under forcing conditions (Pd-C, H_2, 50 bar, 60°C, 5h) in an attempt to ensure complete reaction. In spite of this, some starting material remained (18%). The ^{1}H NMR spectrum of this material revealed that it was a single product, 16α-phenylsulfonyl 17-acetate **18**. Once again, the diagnostic ^{1}H NMR signals of a cycloadduct were observed (Table 2.1). The other signals in the ^{1}H NMR spectrum were remarkably well dispersed, enabling most of them to be assigned. Figure 2.14 shows the high-field region of the ^{1}H NMR spectrum.



Scheme 2.15 *Reagents and conditions*: i, H_2, Pd-C, $CHCl_3$; ii, a) SmI_2-HMPA, THF, -20°C; b) KOH, MeOH, 25°C OR Na-NH_3, THF, -33°C

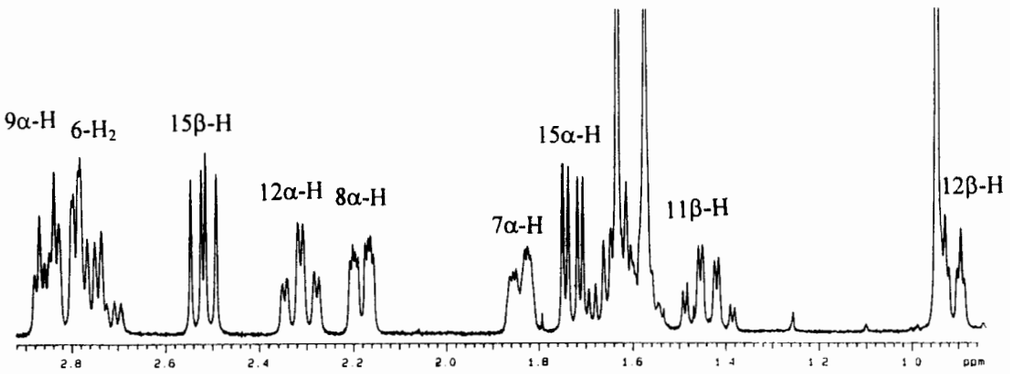


Figure 2.14: ^{1}H NMR spectrum of 16α-phenylsulfonyl 17-acetate **18**

As before, the structure of this cycloadduct, **18**, was ascertained by NOE difference spectroscopy. Irradiation of the 13β-methyl group (δ 0.95) gave a significant enhancement of 16β-H (δ 4.05; 7%), confirming that a β-face cycloaddition had occurred (enhancements of 15β-H, and 11β-H were also observed). Irradiation of 17^2-H (δ 6.0) enhanced the signals for 8α-H (δ 2.2, 6%) and 9α-H (δ 2.9, 7%), as well as the signal for 15α-H (δ 1.7, 1.5%). This, along with the subsequent base treatment of the adduct provided conclusive proof for the assigned structure.

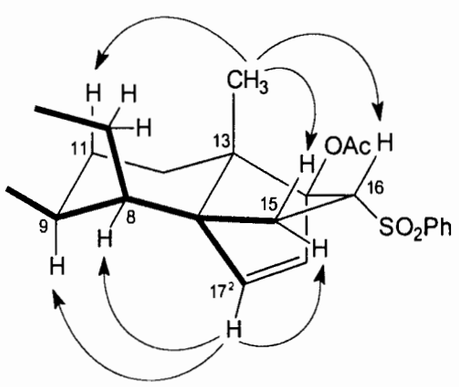


Figure 2.15: Perspective view of the 16α-phenylsulfonyl 17-acetate **18** indicating observed NOE enhancements

Alkaline treatment of this adduct **18**, under identical conditions to those used for the cycloadduct mixture, gave 14β-(phenylsulfonylethyl) Δ^{15} 17-one **21**, identical to that

isolated previously thus confirming both the regiochemistry of the adduct **18** and the stereochemistry of the fragmentation product **21**.

The major product of the hydrogenation reaction was assumed to be a mixture of the 14,17-ethano bridged sulfones **23** and **24** (82%). Recrystallisation afforded what appeared to be a single product from the evidence of ^{1}H NMR analysis. From the recrystallisation recovery (60%), this material was assumed to be the 15α-phenylsulfonyl derivative **24**, but this was not confirmed. The ^{1}H NMR clearly indicated that the double bond had been saturated, with the loss of the AB doublets for 17^1-H and 17^2-H, and the presence of a more complicated signal for 15β-H (δ 3.99, ddd *J* 11.7, 4.3 and 2.4 Hz), with an additional coupling arising from a four-bond 'W-coupling' to 17^2_x-H (Figure 2.16). [85] These data once again indicate that the cycloaddition is *endo* selective, as the *exo* isomer would not display this additional coupling.

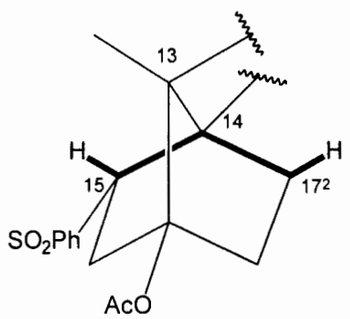


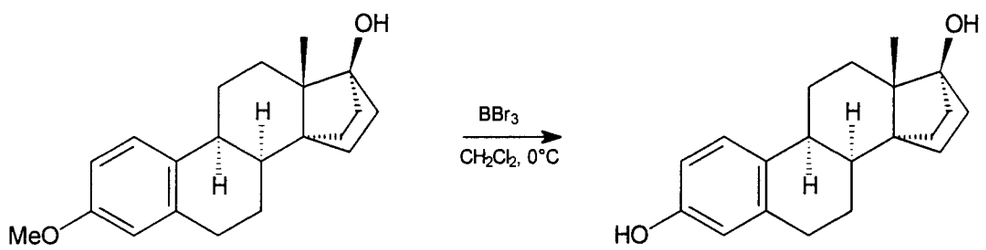
Figure 2.16: A perspective drawing of **24** indicating the W-coupling between 15β-H and 17^2_x-H

Thus, from this combination of experimental and spectroscopic evidence it has been shown that cycloaddition of PVS to the dienyl acetate **16** gives rise to three adducts (79%) in a ratio of approximately 1:1:3 (**17**:**18**:**19**). Possible reasons for this will be discussed later (Section 2.2.3).

Desulfonylation of the mixture of sulfones **23** and **24** was conducted by two different methods (Scheme 2.15). Initial desulfonylation with samarium(II) iodide-hexamethylphosphoramide (HMPA) [86] followed by deacetylation gave 3-methoxy-14,17α-

ethano-8α-estra-1,3,5(10)-trien-17β-ol **25** (78% overall yield) or alternatively treatment with sodium in ammonia [87, 88] gave the same compound in a somewhat diminished yield (53%). The expected absence of definitive downfield signals in the ^{1}H NMR spectrum, along with the remainder of the spectroscopic and analytical data confirmed the structure of the product.

Deprotection at the 3-position was performed using standard conditions [89] (Scheme 2.16) to give the target estradiol analogue **26** which was subjected to biological evaluation. Due to the limited solubility of this material in most organic solvents, full spectroscopic characterisation was not conducted, but the analytical data were consistent with the proposed structure.



25 **26**

Scheme 2.16

Initial microanalyses of **26** gave data consistent with the inclusion of one molecule of methanol (the solvent of recrystallisation). A thermal gravimetric analysis (Figure 2.17) confirmed this, with a distinct loss of solvent between about 65° and 145°C, the major loss occurring between 130°C and 140°C.

The percentage mass loss (5.646%) corresponds to a loss of about 0.5 molecules of methanol, not consistent with the microanalysis, but confirming that solvent has indeed been included. After drying the sample at 120°C for 48h under vacuum, a satisfactory microanalytical result was obtained.

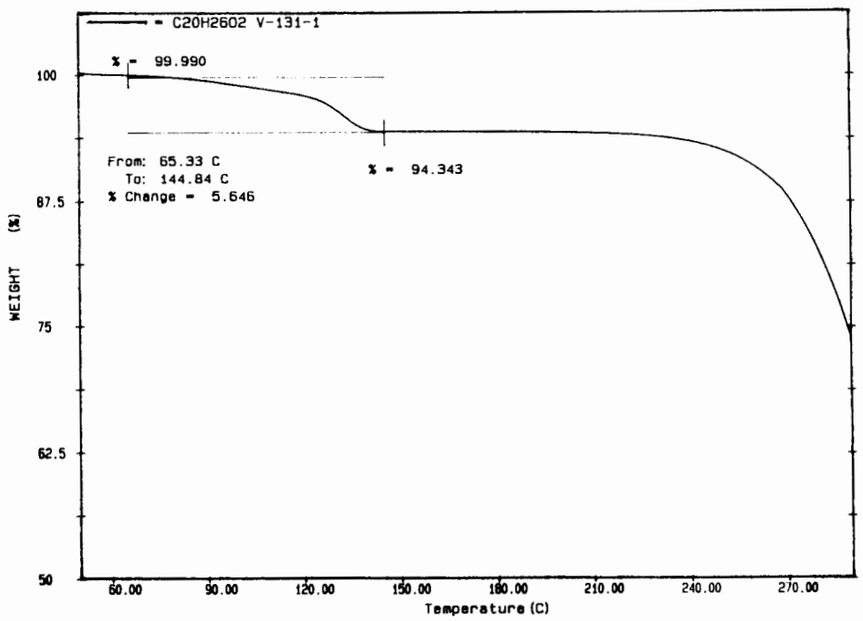


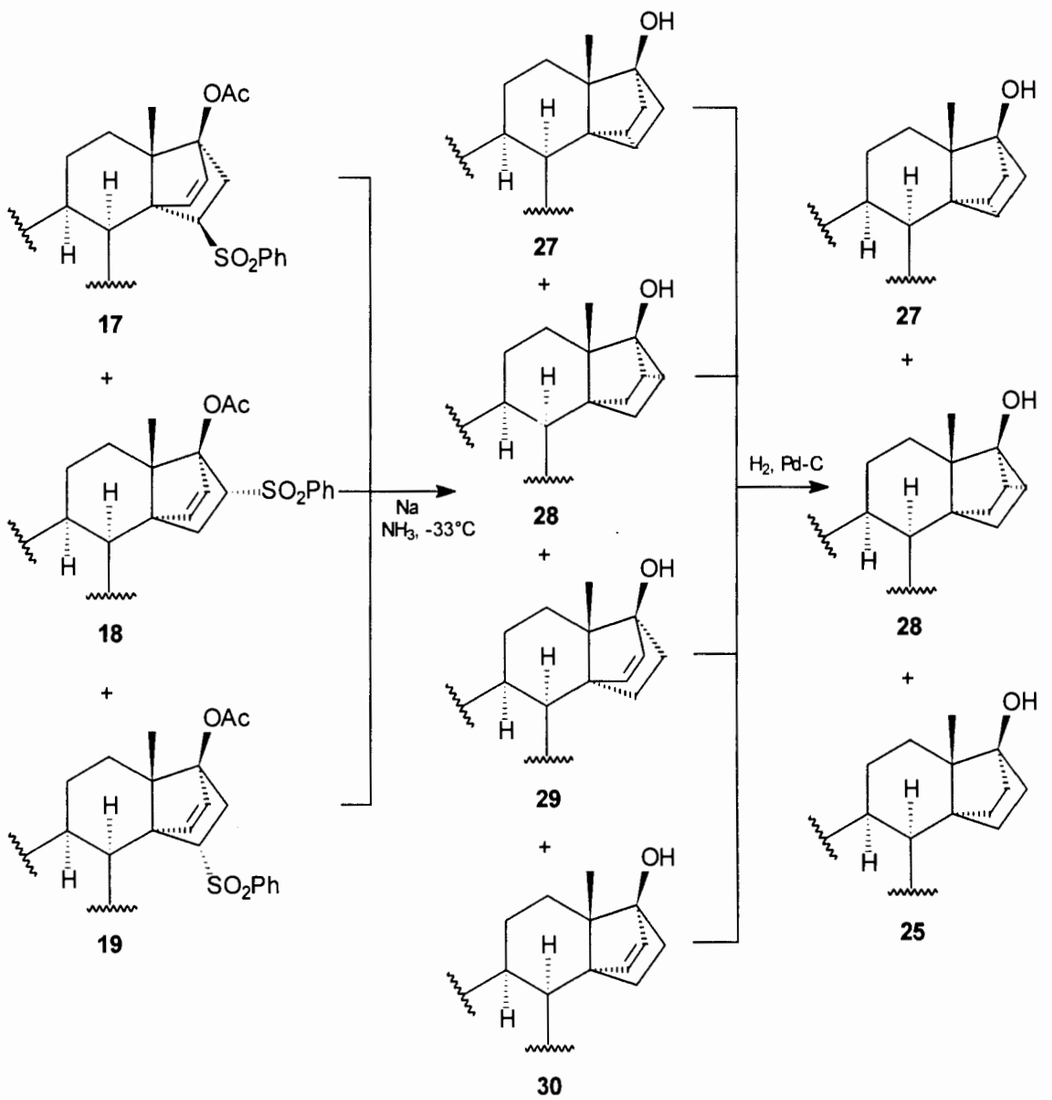
Figure 2.17: Thermal gravimetric analysis of 3,17β-diol **26**

An alternative approach to the target 14α,17α-ethano analogue of 8α-estradiol **26**, involving desulfonylation of the cycloadduct mixture **17**, **18** and **19**, followed by hydrogenation of the resultant etheno bridged compounds, was also investigated for two reasons. Firstly, in the natural series, this route is higher yielding (see Section 2.3) and secondly, it could also provide access to other analogues of 8α-estradiol - the corresponding etheno bridged compounds, and derivatives thereof. [57]

A potential side reaction is the capture of the radical generated by the cleavage of the C-S bond by the olefinic bond, giving rise to a cyclopropyl compound. This process has been well documented in desulfonylation reactions of related steroidal bicyclo[2.2.1]heptenoid systems. [38, 57, 90]

Treatment of the cycloadduct mixture **17**, **18** and **19** with sodium in ammonia gave an inseparable mixture (36%) of the 14,17-etheno bridged products **29** and **30**, and the 15,17^2-cyclo **27** and the 16,17^1-cyclo **28** compounds (Scheme 2.17). The fate of the remainder of the starting material could not be determined. The exact composition of this mixture could not be ascertained, but since no evidence excluding any of the possible

products could be obtained, it was assumed that all four products were present. Clear evidence of a mixture was seen in the duplication of signals for the 13β-Me group (0.97 and 0.98) and 1-H (δ 7.01-7.05). From the two olefinic proton doublets (δ 5.75, *J* 5.9 Hz and δ 5.90, *J* 5.9 Hz) which integrated for approximately one proton combined, it was possible to obtain a rough estimate of the ratio of etheno to cyclo products (*ca* 1:1).



Scheme 2.17

Hydrogenation of this mixture gave a separable mixture of the 14α,17α-ethano compound **25** (48%) and a chromatographically inseparable mixture of the 15,17[2]-cyclo and

16,17^1-cyclo compounds **27** and **28** (52%). The structure of the 14α,17α-ethano compound **25** was assigned by comparison with previously synthesised material, and must originate from the two 14,17-etheno compounds **29** and **30**.

Recrystallisation of the mixture of **27** and **28** afforded a single product which was assigned as the 15,17^2-cyclo compound **27**. This assignment was made on the assumption that the intramolecular radical trapping reaction by the olefinic bond proceeds with similar facility in this series as in the natural series. It has been established that during the desulfonylation of the 16α-phenylsulfonyl derivative in the natural series corresponding to **18**, the amount of 16,17^1-cyclo compound formed is usually in the region of 5%. [57]

Thus it was assumed that the relatively large amount of cyclo compound formed (52%) is due to the radical generated at either C-15 or C-17^2 being sterically hindered, hence promoting the intramolecular reaction with the olefinic bond. Further confirmation of structure was not conducted. No trace of the alternative 16,17^1-cyclo compound **28** was observed, but it is probably present as a minor, unidentified component of the mother liquor material.

In the ^{1}H NMR spectrum of **27** diagnostic signals for the cyclopropyl ring were observed (Figure 2.36); 17^2-H (δ 0.76, dt, *J* 5.8 and 2 x 1.5 Hz), 16α-H and 17^1_n-H (δ 1.44 and 1.48, both dd, *J* 9.7 and 1.5 Hz) and 16β-H and 17^1_x-H (δ 1.81 and 1.90, both dd, *J* 9.7 and 1.5 Hz) which were assigned by analogy (Figure 2.18). [57] The remainder of the spectroscopic and analytical data fully supported this structure.

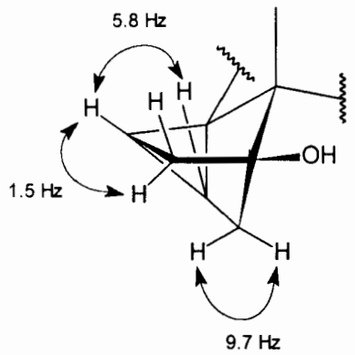


Figure 2.18: Perspective view of 15α,17^2-cyclo compound **27** indicating some of the observed coupling constants (identical values were obtained for the other vicinal and geminal coupling constants in this system, but they have not been indicated for clarity)

This synthetic route does indeed provide access to the target material **26**, however it is not as efficient as that previously described (Scheme 2.15). The desulfonylation step is low yielding and the relatively large amount of 15,17^1-cyclo compound formed further reduces the synthetic utility. This route also failed to provide efficient access to other analogues of 8α-estradiol.

2.2.2 Further cycloaddition reactions of dienyl acetate 16

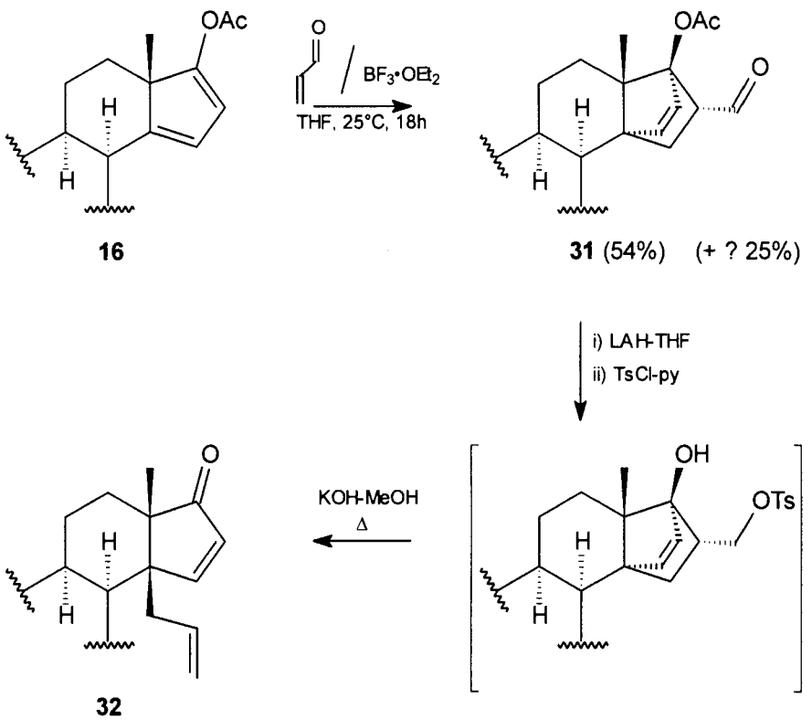
The poor regioselectivity and stereoselectivity observed in the cycloaddition of PVS to dienyl acetate **16** invited speculation on the influence of structural and steric features in the substrate upon the reaction outcome. This is highlighted by the efficient and selective cycloaddition of PVS to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate, [57] in accordance with frontier molecular orbital (FMO) expectations and the well-established preference for β-face entry of conventional dienophiles to this and related 14,16-dienyl systems in the natural steroid series. [91]

The loss of face selectivity in the reaction of the 8α-isomer **16** is not surprising, in view of the change in the steric environment of the 14,16-dienyl moiety. However, the additional manifestation of regioreversal during cycloaddition suggests that the skeletal change may also influence the FMO status of the diene. Furthermore, it may be inferred that the reaction outcome could be influenced by the reactivity and steric demand of the dienophile.

Accordingly, it was considered of interest to conduct cycloadditions of dienyl acetate **16** with a variety of dienophiles, primarily to seek evidence of a trend in reactivity and selectivity, to support a general mechanistic explanation, but also in the hope that synthetically useful cycloadducts could be obtained for further transformation into ring D modified hormone analogues in the 8α-series.

In all of the experiments described in the ensuing section, there was evidence of diminished reactivity and selectivity, by comparison with the natural series, and the interpretation of the results was further complicated by the formation of complex and sometimes inseparable mixtures which made certain structural assignments difficult.

With acrolein, boron trifluoride catalysed cycloaddition to the dienyl acetate **16** (THF, 25°C, 18h), gave a moderate yield (54%) of 17β-acetoxy-3-methoxy-14,17α-etheno-8α-estra-1,3,5(10)-triene-16α-carbaldehyde **31**, along with two other fractions (25% combined) comprising inseparable mixtures of products (Scheme 2.18).



Scheme 2.18

From an examination of the ^{1}H NMR spectrum of **31**, the expected structural features were observed, and are summarised in Table 2.2. These, along with the other spectral and analytical data provided sufficient evidence that a cycloaddition had taken place.

Table 2.2: ^{1}H NMR data for cycloadduct **31**

δ / ppm	Mult.	*J* / Hz	Assignment
1.33	dd	12.4 and 4.1	15α-H
2.45	dd	12.4 and 9.1	15β-H
3.15	ddd	9.1, 4.5 and 4.1	16β-H
6.02	d	6.0	17^2-H
6.36	d	6.0	17^1-H
9.47	d	4.5	16α-C*H*O

The structure of the cycloadduct **31** was assigned from NOE difference spectroscopy and subsequent reactions. Irradiation of the 13β-methyl group enhanced the signals for 16β-H (δ 3.15; 7.5%) and 15β-H (δ 2.45; 2%), amongst others (Figure 2.19). The regiochemistry of the cycloaddition was assigned on the basis of the ready conversion of the adduct **31** into the 14β-allyl Δ^{15} 17-ketone **32** following the reaction sequence developed in the natural series (Scheme 2.18). [33] Reduction of the cycloadduct afforded the 16α-hydroxymethyl 17β-alcohol which was tosylated and subjected to a Wharton fragmentation [92] to give the 14β-allyl Δ^{15} 17-ketone **32** (58%).

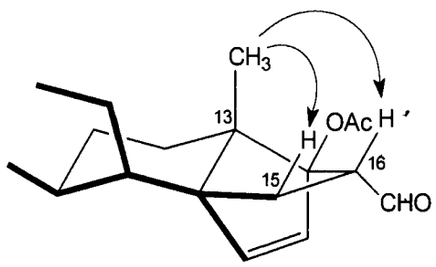


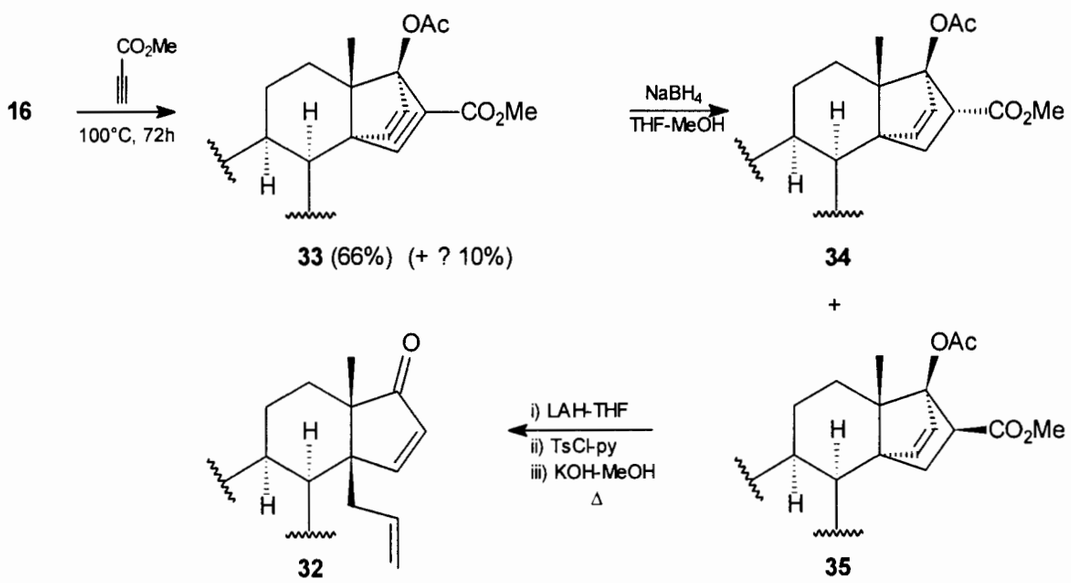
Figure 2.19: Perspective view of 16α-formyl 17-acetate **31** indicating observed NOE enhancements

The 14β-allyl Δ^{15} 17-ketone **32** was readily identified from a comparison of spectral data with the corresponding compound in the natural series. [33] The IR spectrum displayed an absorption band at ν_{max} 1703 cm^{-1}, and the ^1H NMR spectrum, characteristic AB doublets for 16-H (δ 6.15, d, *J* 5.8 Hz) and 15-H (δ 7.50, d, *J* 5.8 Hz), confirming the presence of the cyclopentenone sub-unit. The presence of the 14β-allyl group was indicated by the distinctive ^1H NMR signals (δ 5.08-5.14, 2H, m and δ 5.7-5.8, 1H, m).

The corresponding 14β-allyl Δ^{15} 17-ketone in the natural series [33] is a key intermediate in the synthesis of a number of estradiol analogues. [33, 37] Thus it is envisaged that this compound **32** could be used to synthesise the corresponding 8α-analogues.

The cycloaddition reactions of two other monosubstituted dienophiles (methyl acrylate and nitroethylene; benzene, 100°C) both gave complex, inseparable mixtures which were not characterised.

The cycloaddition of methyl propiolate with dienyl acetate **16** (benzene, 100°C, 120h) gave two fractions (TLC). The minor fraction (10%) was a mixture of products and was not investigated further. The major fraction (66%) was a single product, identified as methyl 17β-acetoxy-3-methoxy-14,17α-etheno-8α-estra-1,3,5(10),15-tetraene-16-carboxylate **33** (Scheme 2.19). Important signals observed in the ^{1}H NMR spectrum of **33** are tabulated (Table 2.3), and together with the analytical data confirmed the gross structure of the adduct.



Scheme 2.19

Table 2.3: ^{1}H NMR data for cycloadduct **33**

δ / ppm	Mult.	*J* / Hz	Assignment
3.72	s		16-CO_2*Me*
6.40	d	5.1	17^2-H
7.05	d	5.1	17^1-H
7.50	s		15-H

An useful feature of the ^{13}C NMR spectrum of this compound, **33**, is that the signal for C-13 (δ 87.4) is significantly downfield, enabling ready identification. A similar deshielding has been observed in the corresponding cycloadduct in the natural series. [38]

As before, the structure of the cycloadduct, **33** was ascertained by NOE difference experiments (Figure 2.20).

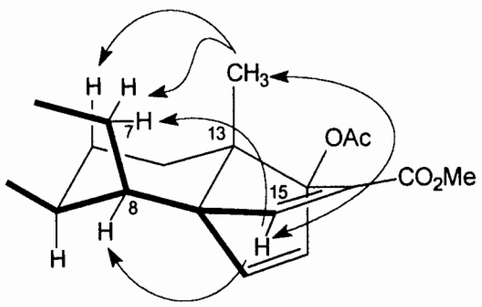


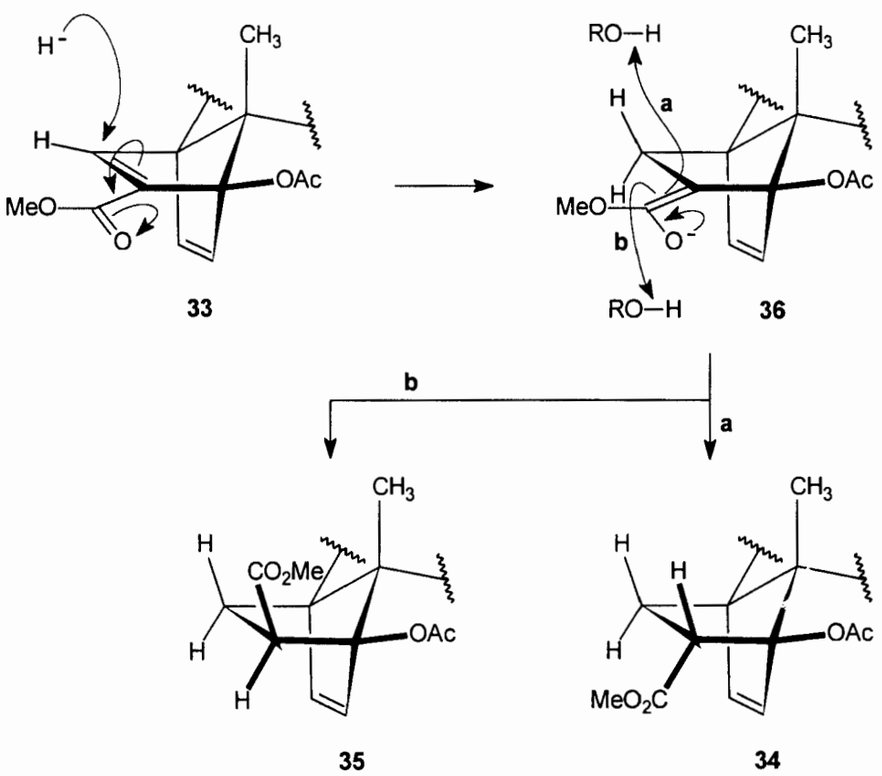
Figure 2.20: Perspective view of 16-methyl carboxylate **33** indicating the observed NOE enhancements

Irradiation of the 13β-methyl group (δ 1.25) enhanced the signal for 15-H (δ 7.5; 1%), amongst others, confirming that a β-face reaction had occurred, while irradiation of 15-H enhanced the signal for 8α-H (δ 2.4; 3%) and 7-H_2 (δ 1.7-1.8; 6%), indicating the regiochemistry of the product.

Chemoselective reduction of the conjugated olefinic bond of the methyl propiolate cycloadduct **33** with sodium borohydride [93] gave two products, assigned as the methyl 16β-carboxylate **35** (47%) and the methyl 16α-carboxylate **34** (22%). Examination of the spectra of the two products clearly indicates that the Δ^{15} bond has been selectively saturated, and the remainder of the spectroscopic and analytical data are consistent with the proposed structures.

The only question to be resolved is the stereochemistry at C-16 of each isomer. It is known that reactions of 7,7-disubstituted bicyclo[2.2.1]heptanoid systems occur preferentially from the α-face. [94, 95] On this basis, the intermediate enolate **36** (Scheme 2.20) would

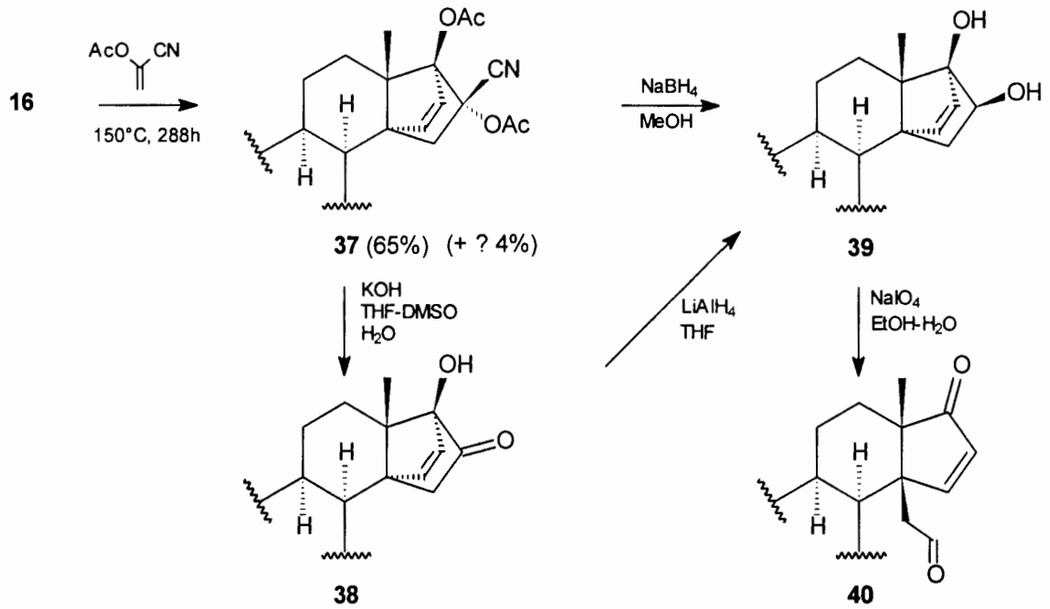
preferentially be protonated from the α-face (pathway **b**) giving methyl 16β-carboxylate **35** as the major product.



Scheme 2.20

Experimental confirmation of the regiochemistry of the cycloadduct **33** was obtained in a similar manner as for the acrolein cycloadduct **31**. The methyl 16β-carboxylate **35** was subjected to the reduction-tosylation-fragmentation sequence to give the 14β-allyl Δ^{15} 17-ketone **32** (46%), identical to that described previously.

Cycloaddition with 2-acetoxyacrylonitrile (benzene, 150°C, 288h) gave two fractions, along with some starting material (13%) despite the regular addition of further dienophile during the course of the reaction (Scheme 2.21). The major fraction (65%) was a single product **37** and was readily separated from the minor fraction (4%), which was an intractable mixture of products and was not characterised.



Scheme 2.21

The major product **37** was readily identified as a cycloadduct from the ^{1}H NMR data, supported by the analytical results. For clarity, key signals in the ^{1}H NMR spectrum have been tabulated (Table 2.4). However, the stereo- and regiochemistry of the product could not be determined from this information.

Table 2.4: ^{1}H NMR data for cycloadduct **37**

δ / ppm	Mult.	*J* / Hz	Assignment
1.62	d	14	15α-H
2.07 and 2.20	both s		16α-OAc and 17β-OAc
3.12	d	14	15β-H
6.02	d	6	17^2-H
6.36	d	6	17^1-H

The assignment of both regio- and stereochemistry was made by NOE difference experiments (Figure 2.21). Irradiation of the 13β-methyl group (δ 1.3) enhanced the signal for 15β-H (δ 3.1; 3.5%) amongst others, clearly showing that the cycloaddition had

occurred from the β-face. Irradiation at 15β-H (δ 3.1) enhanced 7α-H (δ 1.8; 6%), indicating that a head-to-head cycloaddition had occurred. Additionally, irradiating the signal for 17^2-H (δ 6.0) enhanced the signals for 9α-H (δ 2.8; 6%), 8α-H (δ 2.1; 6%) and 15α-H (δ 1.6; 1%), further supporting both assignments. The final structural detail, the relative orientation of the 16-cyano and -acetoxy groups was assigned by analogy to the natural series. [32]

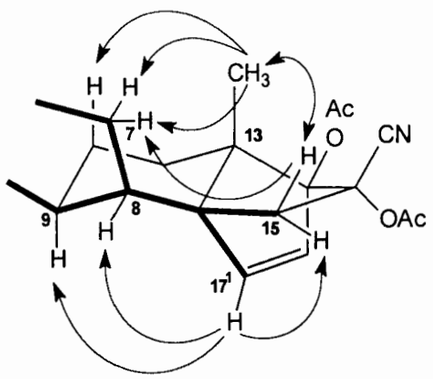
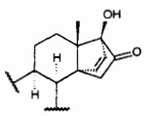
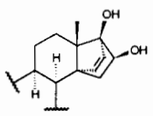
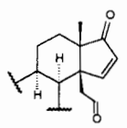


Figure 2.21: Perspective view of 16β-cyano 16α,17β-diacetate **37** indicating the observed NOE enhancements

Conversion of the cycloadduct to the derived 17β-hydroxy 16-ketone **38** and 16β,17β-diol **39**, following the procedures used in the natural series, [32] proceeded uneventfully. Both compounds were readily identified from their spectral characteristics; key ^{1}H NMR data are summarised in Table 2.5.

Table 2.5: Key ^{1}H NMR data for compounds **38-40**

Chemical shift δ/ppm (multiplicity, coupling constant *J*/Hz, assignment)		
 **38**	 **39**	 **40**
δ 1.98 and 2.44 (both d, *J* 16.8, 15α-H and 15β-H), 5.83 and 6.22 (both d, *J* 5.9, 17^2-H and 17^1-H)	δ 3.90 (dd, *J* 7.7 and 2.4, 16α-H), 5.76 and 5.89 (both d, *J* 5.9, 17^2-H and 17^1-H)	δ 2.15 (dd, *J* 16.6 and 1.1, 14^1-H), 3.17 (dd, *J* 16.6 and 2.3, 14^1-H), 6.17 and 7.80 (both d, *J* 6.0, 17^1-H and 17^2-H) and 9.80 (dd, *J* 2.3 and 1.1, 14^1-C*H*O)

The configuration at C-16 of the 16β,17β-diol **39** was assigned by analogy with the natural series where reduction of the corresponding cycloadduct gave the 16β,17β-diol as the major product. [32] Some support for this assignment was obtained from the ^{1}H NMR spectrum. The chemical shift of the 13β-Me (δ 1.17) in the 16β,17β-diol **39** is deshielded relative to the 14α,17α-ethano-8α-17β-alcohol **25** (δ 1.00). The 14,17α-etheno compound was not available for comparison, but in the natural series the chemical shift of the angular methyl is not affected by hydrogenation of the olefinic bond, [57] so this appears to be a reasonable comparison. This deshielding is indicative of a 16β-hydroxy group. The signal for 16α-H (δ 3.90, dd *J* 7.7 and 2.4 Hz), with a large *endo-endo* coupling (to 15α-H) and a smaller *endo-exo* coupling (to 15β-H), does not exclude the alternative configuration at C-16. [32]

Oxidative cleavage of the 16β,17β-diol **39** afforded the 14β-formylmethyl Δ^{15} 17-ketone **40**, thus confirming the assigned regiochemistry, and hence that of the cycloadduct **37**. The structure of this compound, **40**, was confirmed by characteristic spectroscopic data, but it was rather labile, precluding complete characterisation.

Interestingly, compounds **38** and **39** appear to form inclusion compounds with methanol (the solvent of crystallisation), as in the ^{1}H NMR spectra peaks attributable to this solvent were clearly observed (approximately 1:1 ratio of host : guest). Thorough drying (80°C, 48h, high vacuum) enabled acceptable microanalytical data to be obtained.

The results obtained for the cycloaddition reactions of both methyl propiolate and 2-acetoxyacrylonitrile to the dienyl acetate **16** can be explained on steric grounds. For the methyl propiolate cycloaddition, an examination of molecular models clearly indicates that the formation of a β-face and head-to-tail adduct is disfavoured due to steric interactions between the dienophile and the 7,8-bond (Figure 2.22; R = CO_2Me, R' = H). α-Face cycloaddition is also disfavoured as the reagent must approach from the concave face of the diene. On this basis the β-face and head-to-head adduct would be expected to be the major product, and this is indeed what is observed.

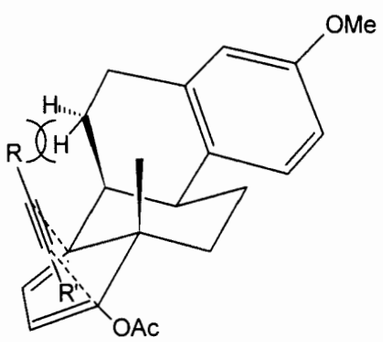


Figure 2.22: Methyl propiolate β-face approach to the dienyl acetate **16**

A similar argument can be used to explain the outcome of the 2-acetoxyacrylonitrile cycloaddition. As can be seen from Figure 2.23, a β-face and head-to-tail approach of the dienophile suffers from severe steric hindrance (R, R' = OAc, CN). α-Face cycloaddition is again disfavoured as the dienophile is required to approach from the more hindered, concave face, so one would expect the β-face and head-to-head adduct to predominate, as is indeed observed.

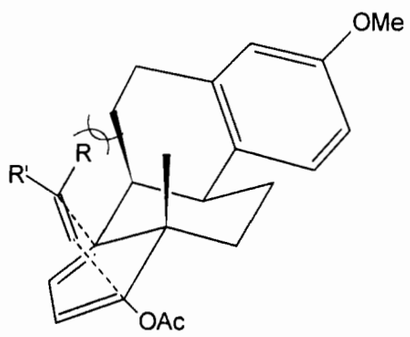
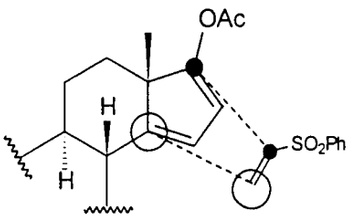


Figure 2.23: 2-Acetoxyacrylonitrile β-face and head-to-tail approach to the dienyl acetate **16**

The monosubstituted dienophiles (PVS, nitroethylene and methyl acrylate) all display a similar pattern of multiple cycloadducts. As the results for both nitroethylene and methyl acrylate could not be quantified the result for PVS will be used for the purpose of this discussion.

An examination of molecular models reveals no major steric impediment to a β-face and head-to-tail cycloaddition reaction (Figure 2.23; R = H, R' = SO_2Ph). The α-face remains sterically disfavoured, but with a monosubstituted dienophile, the steric effects will be minimised. Thus, β-face addition should be favoured on these grounds, but there are no obvious steric factors influencing the regiochemistry.

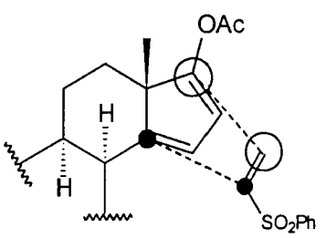
From an FMO perspective, the regiochemistry of the reaction is dependent on the nature of the groups at C-14 and C-17. [96] If it is assumed that the influence of these groups in the 8α-series is similar to that observed in the natural series, where the effect of the electron donating 17-acetate [97] predominates over that of the electron-donating C-14 substituent (on the basis of experimental results, Figure 2.24), [98] then the selective formation of head-to-head adducts is predicted. From the results, β-face selectivity (4:1) is indeed observed, but the predicted regioselectivity is incorrect, as head-to-tail adducts are favoured over head-to-head adducts (4:1).



----- bond forming

Figure 2.24: Cycloaddition of PVS to 3-methoxyestra-1,3,5(10),14,16-pentaen-17-yl acetate, indicating the $HOMO_{diene}$-$LUMO_{dienophile}$ interaction assumed to be responsible for the regioselectivity observed

It therefore appears as though inversion at C-8 in the dienyl acetate moiety increases the electron donating ability of the C-14 group, overriding the effect of the 17-acetate on the frontier orbitals (Figure 2.25). This would lead to the preferential formation of head-to-tail adducts, as observed. However, as the orbital coefficients of either diene have not been calculated, this hypothesis cannot be verified.



----- bond forming

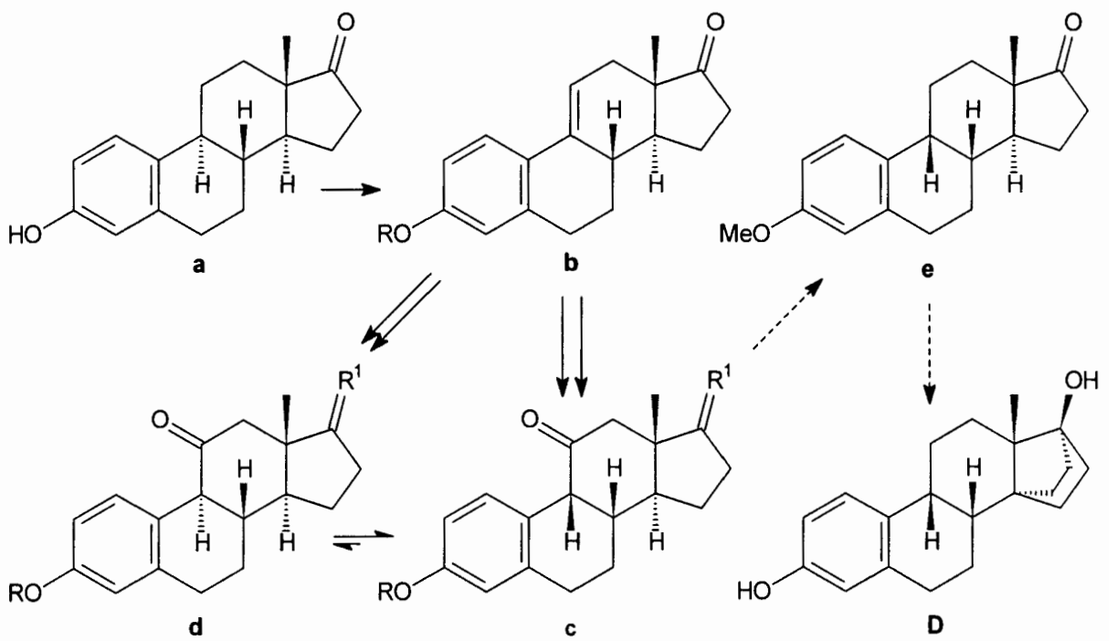
Figure 2.25: Cycloaddition of PVS to dienyl acetate **16**, indicating the $HOMO_{diene}$-$LUMO_{dienophile}$ interaction assumed to be responsible for the regioselectivity observed

The addition of a Lewis acid to a 'normal' cycloaddition reaction is known to polarise the LUMO of the dienophile, thus enhancing the selectivity inherent in the uncatalysed reaction. [99] However, this does not account for the reversal of regioselectivity observed for the Lewis acid catalysed cycloaddition of acrolein to the dienyl acetate **16**, where the head-to-head adduct **31** is the major product. Further work is required to explain this observation.

From these results, some conclusions can be drawn about cycloaddition reactions of the dienyl acetate **16**. Sterically hindered dienophiles display a similar reaction pattern to that observed in the natural series, with somewhat diminished yield. A combination of subtle steric and stereo-electronic factors results in a loss of regio- and stereoselectivity for monosubstituted dienophiles. Further work is warranted to explore the role of Lewis acid catalysis upon cycloaddition reactions to this diene so as to explain the reversal of regioselectivity observed.

2.3 9β-Series

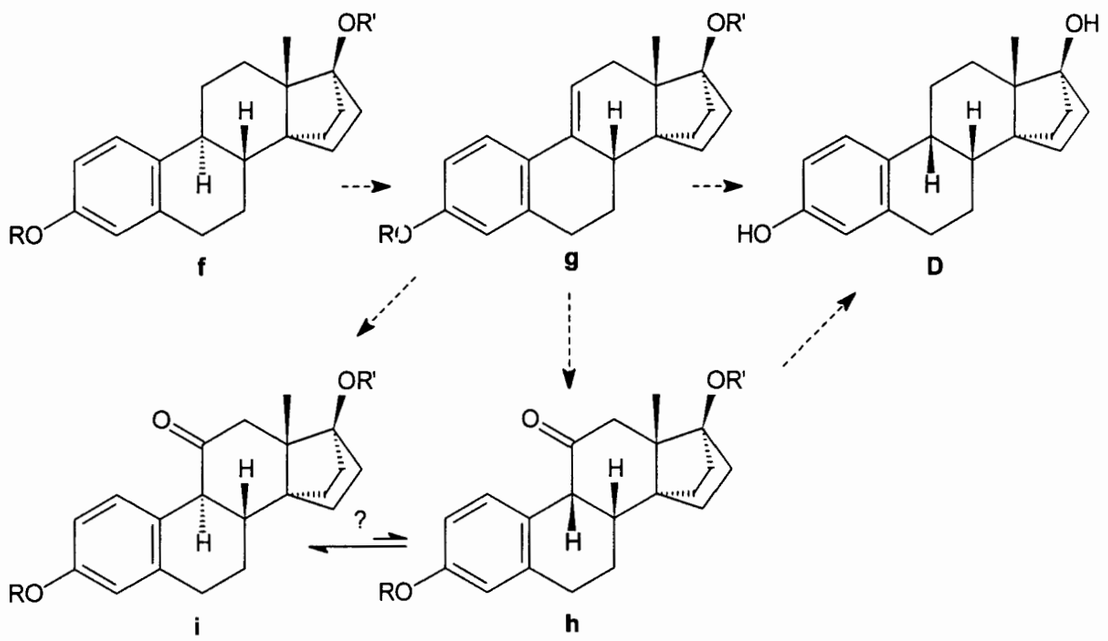
Two possible synthetic routes towards the target, 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diol **D**, were investigated. The first approach involved inversion at C-9 of estrone, followed by incorporation of the ethano bridge using methodology similar to that described for the 8α-series (Section 2.2) (Scheme 2.22).



Scheme 2.22: Planned synthetic route

In this regard, the first key intermediate is the $\Delta^{9(11)}$-compound **b** which is readily available from estrone **a**. [100-105] Configurational inversion at C-9 can then be achieved by one of two alternate methods, *viz.* (i) hydroboration followed by oxidation to give the 11-ketone **d** [100, 105] which is readily equilibrated to the 9β*H*-11-ketone **c** [100, 106] or (ii) epoxidation followed by a Lewis acid catalysed 1,2-hydride shift to give the 9β*H*-11-ketone **c**. [100] Deoxygenation of the 9β*H*-11-ketone **c** should then provide the desired 9β-derivative **e**, further modification of which, along similar lines to the 8α-series (Section 2.2), namely cycloaddition of an ethylene equivalent to the derived dienyl acetate followed by subsequent modification, would provide the target material **D**.

The alternative approach explored was inversion at C-9 of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol **A** (or a suitable derivative) (Scheme 2.23). The first key intermediate is the $\Delta^{9(11)}$-derivative **g**, which should be available from the 14,17α-ethanoestratriene **f** utilising similar reaction conditions to those envisaged for the unbridged series. The hydroboration-oxidation sequence described for the unbridged series (Scheme 2.22) should provide the 11-ketone **i**, however equilibration (**i-h**) is unlikely to lead to the desired 9β*H*-11-ketone **h**.



Scheme 2.23: Planned synthetic route

As indicated in Scheme 2.22, the equilibration of **d** favours the 9β*H*-11-ketone **e**. Replacing the 14α-H of **d** with a 14α-methyl group has been shown both by calculations and experimental findings to distort this equilibrium in favour of the 9α*H*-11-ketone. [55] The 14,17α-ethano bridge is expected to be at least as sterically demanding as a 14α-methyl group, so it is unlikely therefore that equilibration of the 9α*H*-11-ketone **i** would provide any 9β*H*-11-ketone **h**.

The epoxidation-hydride shift reaction sequence could provide access to the 9β*H*-11-ketone **h**, but the 14α,17α-ethano bridge is expected to influence the α-selective

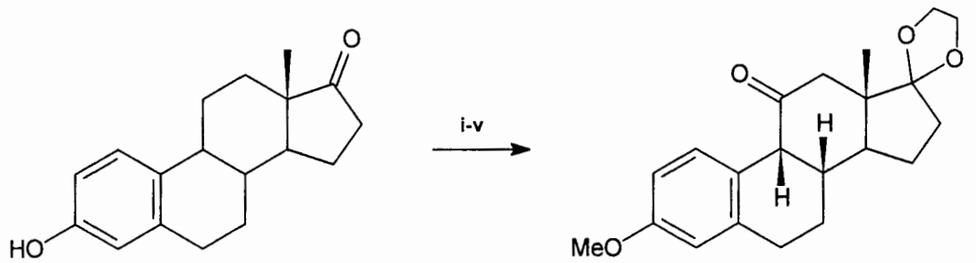
epoxidation observed in the natural series, resulting in a diminished yield of the desired product **h** accompanied by the isomeric 9α*H*-11-ketone **i**. With the 9β*H*-11-ketone **h** in hand, subsequent deoxygenation and further modification would provide the target material **D**.

An alternative, more direct, approach to the unnatural stereocentre is via hydrogenation of the $\Delta^{9(11)}$-olefin **g** in the expectation that the 14α,17α-ethano bridge would diminish the α-face selectivity observed in the natural series, [107-109] thus providing the target molecule **D**. A similar reduction of α-face selectivity has been observed in the hydrogenation of other 14α-substituted $\Delta^{9(11)}$-olefins, for example 17β-*t*-butoxy-3-methoxy-14α-methylestra-1,3,5(10),9(11)-tetraene [29] and 14,17α-ethylidenedioxy-3-methoxy-19-norpregna-1,3,5(10),9(11)-tetraen-20-one. [110]

The results of these two investigations will be presented in the next section.

2.3.1 Synthesis of 3-methoxy-9β-estra-1,3,5(10)-trien-17-one

17,17-Ethylenedioxy-3-methoxy-9β-estra-1,3,5(10)-trien-11-one **42** was synthesised from estrone **41** according to the procedure of Collins and Sjövall [100] (15% overall yield, Scheme 2.24). To summarise, estrone **41** was selectively dehydrogenated with DDQ to give the $\Delta^{9(11)}$-olefin. Both oxygen functionalities were then protected (3-O-methylation followed by 17-ketalisation). Stereoselective epoxidation gave the 9α,11α-epoxide, which after undergoing a 1,2-hydride shift yielded the 9β*H*-11-ketone **42**.

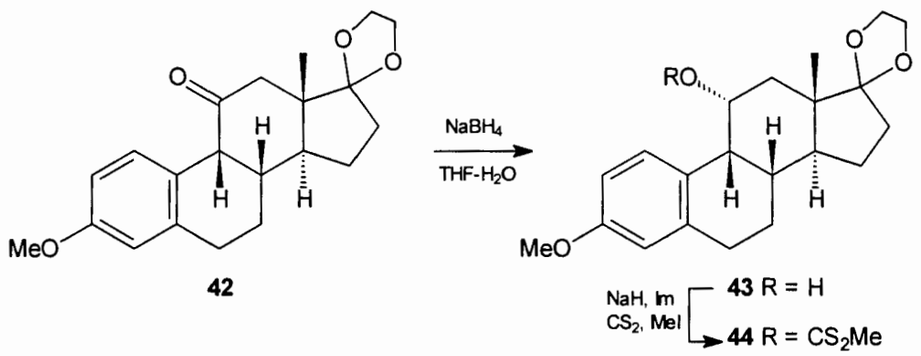


41 **42**

Scheme 2.24 *Reagents and conditions*: **i**, DDQ, MeOH, 25°C; **ii**, Me_2SO_4, K_2CO_3, acetone, 25°C; **iii**, $(CH_2OH)_2$, *p*-TsOH, PhH, Δ; **iv**, *m*-cpba, $NaHCO_3$, CH_2Cl_2-H_2O, 25°C; **v**, $LiClO_4$, PhH, Δ

Attempts at direct deoxygenation of the 11-ketone **42** (dithioketalisation-desulfurisation, [111] or Wolff-Kishner) [112] were unsuccessful with complex mixtures of products being isolated. Thus the use of an indirect method for accomplishing this transformation was investigated.

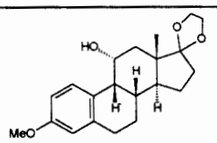
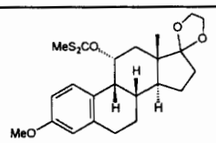
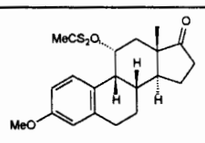
Reduction of the 11-ketone **42** with sodium borohydride in aqueous THF gave exclusively the 11α-alcohol **43** (Scheme 2.25). Similar selectivity has been observed in the reduction of other 17,17-ethylenedioxy-9β-estra-1,3,5(10)-trien-11-ones. [113] A comparison of the ^{1}H NMR spectrum of **43** with that previously reported [100] provided conclusive structural proof. The signal for 1-H (δ 7.77, d, *J* 8.5 Hz) is diagnostic for the configuration at C-11, as in both the natural and 9β-series the 11α-hydroxy group is in close proximity with 1-H, causing a significant deshielding (*ca.* 0.5 ppm) of the signal for 1-H relative to the 11β-epimer. [100]

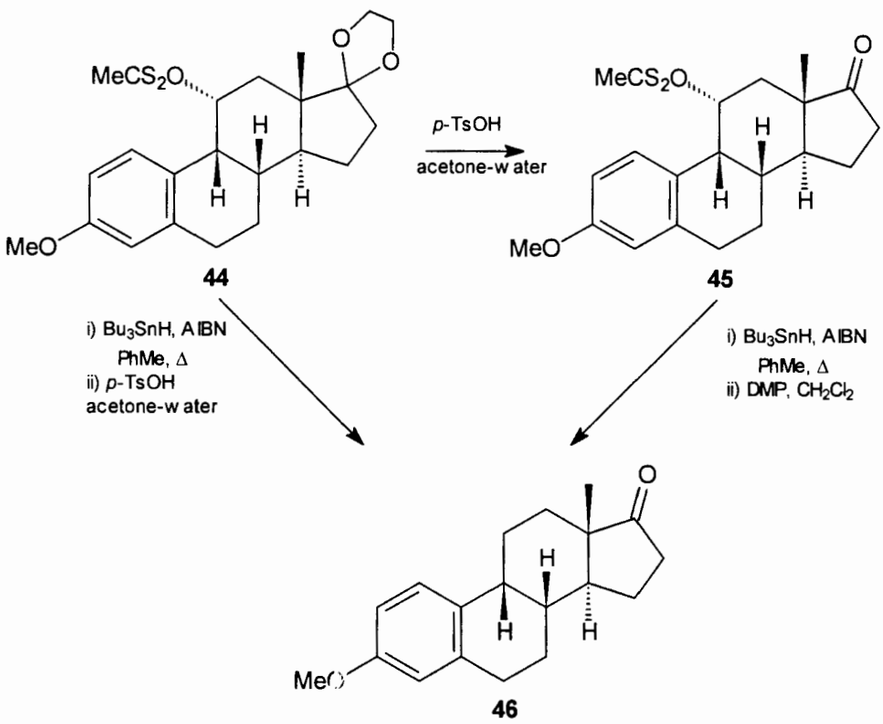


Scheme 2.25

Conversion of the 11α-alcohol **43** into the 11α-xanthate **44** for Barton-McCombie deoxygenation [114] was accomplished utilising standard methodology (74%). [114] Some loss of the 17-ketal, to give the 17-ketone **45**, was observed on storage. Alternatively, this deprotection could readily be accomplished by stirring the 17-ketal **44** with toluene-*p*-sulfonic acid in aqueous acetone giving the 17-ketone **45** (85%). The important ^{1}H NMR signals and coupling constants used to identify these compounds are summarised in Table 2.6.

Table 2.6: Table of important ^{1}H NMR features of 9β-estratrienes **43-45**.

	Chemical shift δ/ppm (multiplicity, coupling constant *J*/Hz)		
Proton	 **43**	 **44**	 **45**
9β-H	δ 3.13 (br m)	δ 3.50 (t, *J* 4.3)	δ 3.50 (t, *J* 4.7)
11β-H	δ 4.45 (dt, *J* 7.5 and 2 x 4.6)	δ 6.30 (dt, *J* 10.9 and 2 x 4.3)	δ 6.31 (dt, *J* 8.3 and 2 x 4.6)
1-H	δ 7.77 (d, *J* 8.5)	δ 7.61 (d, *J* 8.5)	7.51 (d, *J* 8.5)



Scheme 2.26

Refluxing the 17,17-ethylenedioxy-11α-xanthate **44** with tributylstannane and α,α'-azobis(isobutyronitrile) (AIBN) in toluene, [114] followed by deprotection at C-17 gave the desired 3-methoxy-9β-estra-1,3,5(10)-triene-17-one **46** (28%). Alternatively, deoxygenation of the 17-oxo-11α-xanthate **45** followed by reoxidation at C-17 [with the Dess-Martin periodinane (DMP)] [72] gave the same product **46** (14%). This compound is known, [115] but the only information available was an optical rotation, which was comparable to that measured. Thus, a detailed NMR analysis of the 9β 17-ketone **46** was conducted; all data were consistent with the structure. Table 2.7 shows extensive assignments of the ^{1}H NMR spectrum. Figure 2.27 shows a perspective view of the 9β 17-ketone **46**.

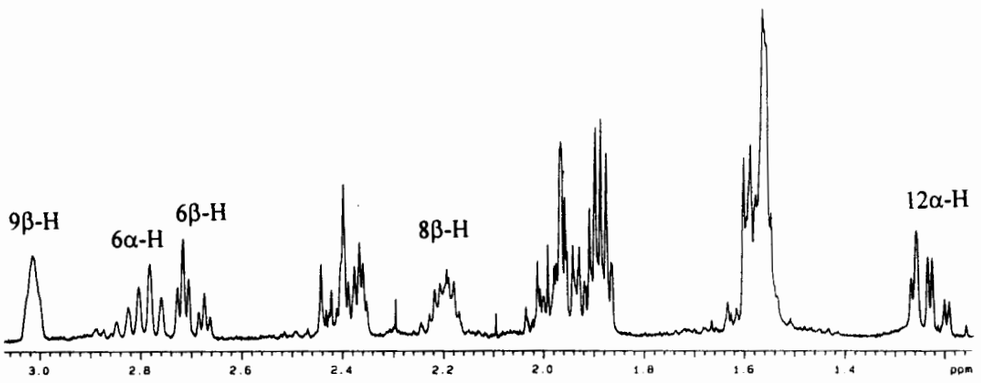


Figure 2.26: High field region of ^{1}H NMR spectrum of the 9β 17-ketone **46**.

Table 2.7: ^{1}H NMR assignments of the 9β 17-ketone **46**

δ / ppm	Int.	Mult.	*J* / Hz	Assignment
0.97	3H	s		13β-Me
1.24	1H	td (obsc.)	2 x 12.8 and 3.8	12α-H
1.54-1.61	2H	m (obsc.)		12β-H and 14α-H
1.86-2.04	6H	m (obsc.)		7-H_2, 11-H, 15-H_2 and 16-H
2.20	1H	m (obsc.)		8β-H
2.34-2.42	2H	m (obsc.)		11-H and 16-H
2.70	1H	dt	16.8 and 2 x 4.6	6β-H
2.80	1H	td	2 x 16.8 and 8.8	6α-H
3.01	1H	br m	$W_{½}$ 10 Hz	9β-H
3.77	3H	s		3-OMe
6.62	1H	d	2.7	4-H
6.72	1H	dd	8.6 and 2.7	2-H
7.22	1H	d	8.6	1-H

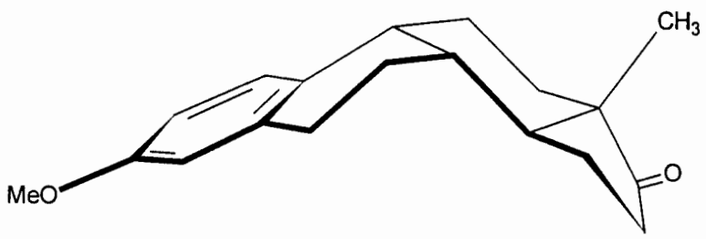


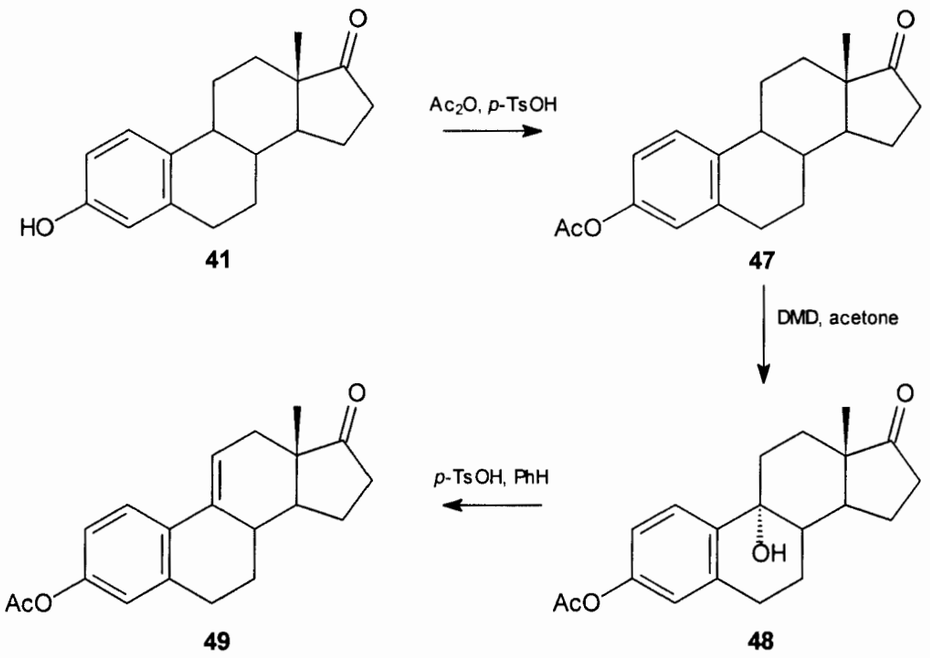
Figure 2.27: Perspective view of the 9β 17-ketone **46**

Diagnostic features in the ^{1}H NMR spectrum of the 9β 17-ketone **46** are the broad, unresolved signal for 9β-H (δ 3.01) and the separation of the signals for the two hydrogens on C-6, which generally appear as an unresolved two proton multiplet in the natural series.

Although this reaction sequence provided access to the desired 3-methoxy-9β-estra-1,3,5(10)-trien-17-one **46**, the overall yield from estrone **41** was *ca.* 2%; thus it is not a synthetically viable route for the large-scale preparation of this material. In order to improve the overall conversion from estrone **41**, the optimisation of some of the low-yielding steps was attempted.

The first step to be investigated was the introduction of the $\Delta^{9(11)}$-bond. Although the DDQ oxidation affords a reasonable yield (*ca.* 80%) of the desired product, the reaction is capricious and invariably some starting material remains. Separation of this from the $\Delta^{9(11)}$-compound is difficult, so it has to be carried through the synthetic sequence, until it can be readily separated from the 9β*H*-11-ketone **42**.

A number of other methods have been reported for the introduction of a $\Delta^{9(11)}$-bond into the estratriene skeleton. [101-104] Of these, the only one which could be reproduced was the dimethyldioxirane (DMD) 9α-hydroxylation-dehydration reaction sequence (Scheme 2.27). [101, 102]



Scheme 2.27

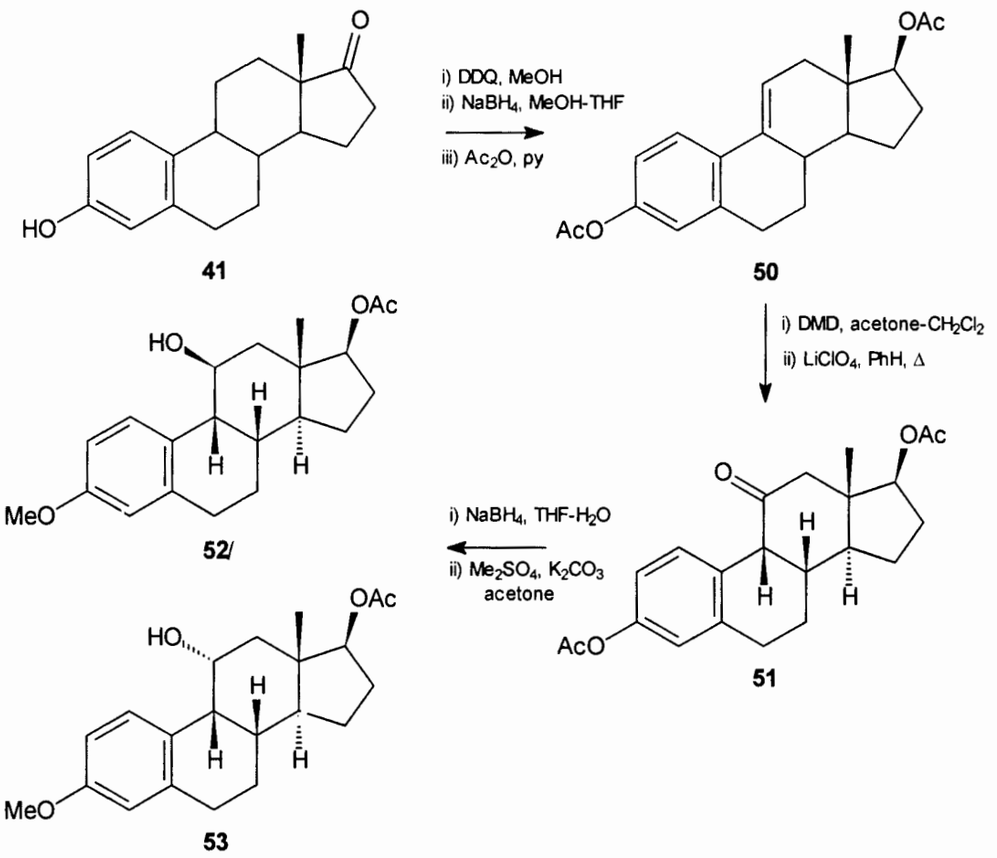
Estrone **41** was acetylated, giving estrone 3-acetate **47**, which was treated with DMD generated *in situ* [116] (oxone ® and acetone in a pH 7 buffered water-dichloromethane mixture) to give of the desired 9α-alcohol **48** (30%), along with starting material **47** (52%). Dehydration of the 9α-alcohol **48** with toluene-*p*-sulfonic acid in benzene afforded the $\Delta^{9(11)}$-compound **49** (65%). Alternatively, treatment of the 3-acetate **47** with an isolated solution of DMD in acetone [101] (prepared by the method of Adam *et al*) [117] followed by dehydration gave the desired $\Delta^{9(11)}$-compound **49** (35% overall yield). Both yields were substantially inferior to that obtained in the DDQ reaction, and despite all attempts, the reported yields (80%) [101, 116] for this transformation could not be reproduced. Thus, the attempted optimisation of this stage of the synthesis was discontinued.

The next step of the synthetic sequence to be investigated was the epoxidation-rearrangement of the $\Delta^{9(11)}$-olefin to the 9β*H*-11-ketone **42**. The instability of the intermediate 9,11α-epoxy-17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-triene to acidic conditions, led to a significant amount of decomposition, despite the buffered medium in which the reaction was conducted. [100]

In an attempt to overcome this problem, the protecting group at C-3 was changed from a methyl ether to an acetate, as this is reported to increase the stability of the resultant 9α,11α-epoxide. [100] The extremely mild epoxidising reagent, DMD [118, 119] was used instead of a peracid in order to keep the reaction at neutral pH. This necessitated a change of protecting group at C-17, as DMD is known to convert ketals to ketones. [120]

Thus, DDQ oxidation of estrone **41** [100] followed by sodium borohydride reduction of the $\Delta^{9(11)}$ 17-ketone and acetylation of the resultant $\Delta^{9(11)}$ 3,17β-diol, gave the $\Delta^{9(11)}$ 3,17β-diacetate **50** (90%) (Scheme 2.28). A comparison of the physical properties with those reported [103, 121] and careful examination of the ^{1}H NMR spectrum of this material indicated the presence of a small amount (*ca.* 10%) of estra-1,3,5(10)-triene-3,17β-diyl diacetate. This was confirmed by subsequent reactions.

Treatment of the $\Delta^{9(11)}$ 3,17β-diacetate **50** with DMD in acetone led to a rapid conversion into the 9α,11α-epoxide, which was not isolated, but was treated directly with lithium perchlorate in refluxing benzene [100] to give the 9β*H*-11-ketone **51** (50%). The configuration at C-9 was assigned from a comparison of the ^{1}H NMR signal for 9β-H (δ 3.62, d, *J* 5.2 Hz), with literature values. [100, 106] It has been established that for simple 11-oxoestra-1,3,5(10)-trienes, the signal for 9α-H displays a coupling constant of *ca* 12Hz and the signal for 9β-H displays a coupling constant of *ca* 5Hz. [100, 106] The remainder of the spectroscopic data supported the assigned structure. Also isolated from this reaction was estra-1,3,5(10)-triene-3,17β-diyl diacetate (13%).

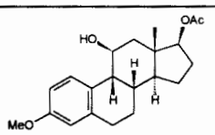
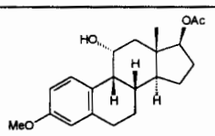


Scheme 2.28

Reduction of the 11-ketone **51** with sodium borohydride, followed by 3-O-methylation gave a separable mixture of the isomeric 11-alcohols **52** (28%) and **53** (46%). This result contrasts with the reduction of the 17,17-ethylenedioxy 9β*H*-11-ketone **42** which provides exclusively the 11α-hydroxy derivative **43**. A satisfactory explanation for this loss of stereoselectivity has not been found.

The 11-alcohols **52** and **53** were readily separated and identified from a comparison of ^{1}H NMR data with those reported for the 17,17-ethylenedioxy-3-methoxy-9β-estratriene-11ξ-ols. [100] The signal for 1-H in the 11α-alcohol **53** was significantly deshielded relative to the equivalent signal in the 11β-alcohol **52** (Table 2.8). Also apparent was the deshielding of the 13β-methyl group of the 11β-alcohol **52** under the known influence of the 1,3-diaxial relationship between 11β-OH and 13β-Me.

Table 2.8: ^{1}H NMR data for the 11-alcohols, **52** and **53**

	Chemical shift δ/ppm (multiplicity, coupling constant *J*/Hz)	
Proton(s)	 **52**	 **53**
13β-Me	δ 1.05 (s)	δ 0.91 (s)
9β-H	δ 2.40 (br d, *J* 10.6)	δ 3.11 (t, *J* 4.5)
11-H	α-H, δ 4.6-4.7 (m)	β-H, δ 4.38 (dt, *J* 8.1 and 2 x 4.5)
1-H	δ 7.16 (d, *J* 8.6)	δ 7.86 (d, *J* 8.6)

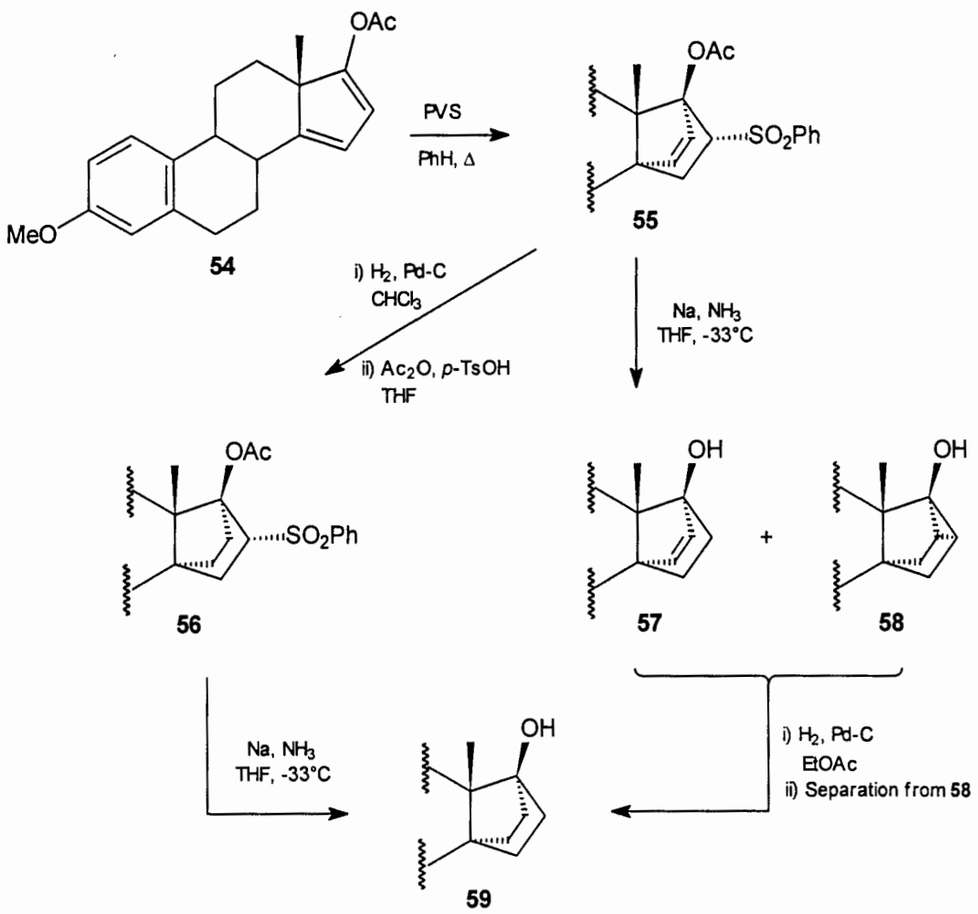
Using this modified reaction sequence, the overall conversion from estrone **41** to an 11-alcohol (**52** and **53**) is 33%, significantly better than the previous yield of *ca.* 15%. However, the need to perform further reactions on either a mixture of compounds **52** and **53**, or on the two derivatives separately complicates the reaction sequence, thus it was discontinued.

In conclusion, a synthetic route to 3-methoxy-9β-estra-1,3,5(10)-trien-17-one **46** has been developed. The poor overall conversion from estrone (*ca.* 2%) led to an investigation into the optimisation of several of the steps in this route. The yield for the dehydrogenation step was not improved by the alternative methods investigated. The epoxidation-rearrangement sequence was improved, with the overall yield of 9β*H*-11-ketone (from estrone **41**) increasing from 15% to 45%. The subsequent conversion of the 9β*H*-11-ketone into an 11-alcohol did not occur as selectively as in the initial sequence, due to the different protecting groups employed in order to improve the yield of the synthesis. This is a significant disadvantage and led to this, otherwise promising, route being discontinued.

2.3.2 Synthesis of 14,17α-ethano-9β-estra-1,3,5(10)-trien-17β-ol

As the attempted synthesis of the target molecule **D** via inversion at C-9 followed by introduction of the 14,17-bridge was rendered impractical by the low conversion of estrone **41** into 9β-estrone 3-methyl ether **46**, the alternative approach of inversion at C-9 of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol (or a suitably protected derivative) was investigated.

The starting material utilised in this study was 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol **59**. [57] The synthesis of this material will be briefly outlined (Scheme 2.29)



Scheme 2.29: Preparation of 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol **59**

Cycloaddition of the dienyl acetate **54** with PVS proceeded to give the adduct **55**, as reported. [57] Two approaches towards the desired product **59** are possible, either via hydrogenation followed by desulfonylation, or via the reverse sequence. In the latter route, the desulfonylation reaction is known to afford a small quantity (*ca.* 5%) of the 16α,17[1]-cyclo compound **58** [57] making an additional separation step essential.

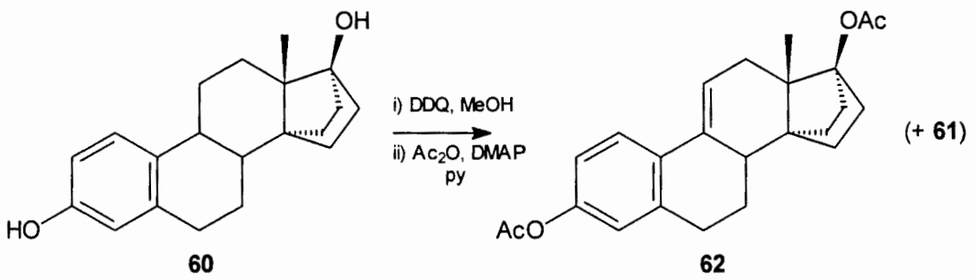
Large-scale (> 1 g) hydrogenation of the cycloadduct **55**, using the reported conditions (Pd-C, 1 atm. H_2, ethyl acetate, 25°C), [57] was found to be impractical, with mixtures of the cycloadduct **55** and the dihydro compound **56** being formed, possibly due to catalyst deactivation. The insolubility of the cycloadduct **55** in ethyl acetate necessitated the use of a large solvent volume, a further complicating factor. However, this was overcome by performing the reaction under more forcing conditions, and changing the solvent (Pd-C, 50 bar H_2, chloroform, 75°C). Some loss of the 17β-acetoxy group was observed under these conditions, however reacetylation of the crude reaction mixture gave the dihydro compound **56**. Desulfonylation [87, 88] of the dihydro compound **56** gave the desired product **59** in 70% overall yield from the cycloadduct **55**.

Alternatively, desulfonylation of the cycloadduct **55** followed by hydrogenation gave the desired product **59** in 77% yield, which was separated from the 16α,17[1]-cyclo compound **58** (9%) by a combination of recrystallisation and chromatography.

Although the latter route affords a slightly higher yield of the desired product **59**, the need to separate it from the 16α,17[1]-cyclo compound **58** makes this route less attractive; thus the former is the method of choice for this conversion.

The first key intermediate is the $\Delta^{9(11)}$-compound (Scheme 2.23, **g**). The synthesis of this material was explored, using the procedures established for the unbridged series (Section 2.3.1). Treatment of the 3,17β-diol **60** (synthesised by deprotection [57, 89] of the 3-methyl ether **59**) with DDQ, followed by acetylation gave a *ca* 2:1 mixture of the $\Delta^{9(11)}$-olefin **62** and the saturated diacetate **61** (a ^{1}H NMR estimate from the signals for 1-H, at δ 7.30 for **61** and δ 7.66 for **62** respectively) which was inseparable by either silica gel chromatography or selective crystallisation (from either methanol or acetone-hexane)

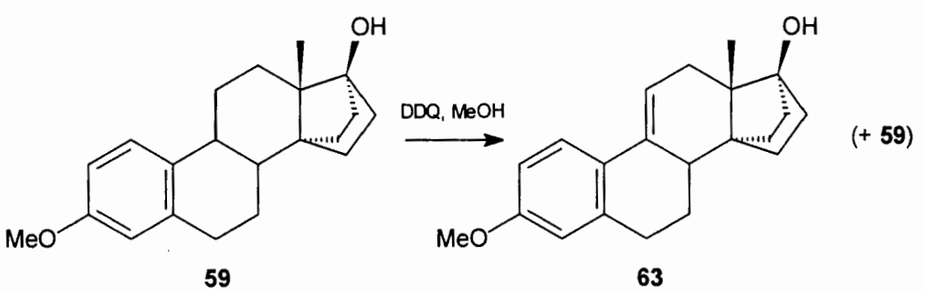
(Scheme 2.30). The use of protecting groups for the two hydroxy functionalities was necessitated by the extreme insolubility of the 3,17β-diol **60**, (and the resultant $\Delta^{9(11)}$ 3,17β-diol) in most solvents, and attendant handling problems.



60 **62**

Scheme 2.30

Alternatively, DDQ oxidation of 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol **59** gave an inseparable mixture of the starting material **59** and the $\Delta^{9(11)}$ derivative **63** (*ca* 1:1 by ^{1}H NMR; judged by the signals for 1-H - δ 7.2 for **59** and δ 7.6 for **63**) (Scheme 2.31). This result is comparable to that observed in the unbridged series. [100]



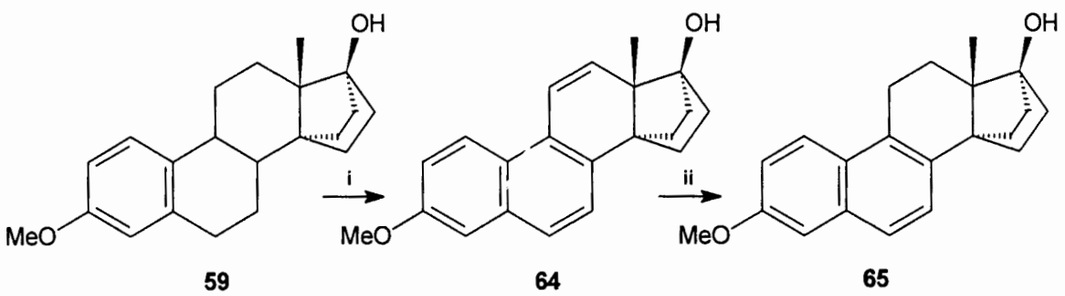
59 **63**

Scheme 2.31

Allowing the reaction to proceed for longer periods (18h) did not increase the amount of $\Delta^{9(11)}$-product **63** in the reaction mixture, and from an examination of the ^{1}H NMR spectrum of this mixture, signals attributable to 3-methoxy-14,17α-ethanoestra-1,3,5(10),6,8-pentaene-17β-ol **65** (subsequently synthesised, see Scheme 2.32) were observed.

Attempts at separating these two compounds (**59** + **63**) by derivatisation were unsuccessful; neither the derived 17β-acetates nor the 17β-*t*-butyldimethylsilyl ethers were separable on silica gel chromatography or by crystallisation.

In an attempt to improve this reaction, the use of an acid catalyst was investigated. The use of acid to modify the reactivity of DDQ is well-documented, [122] for example steroidal Δ^4-3-ketones are dehydrogenated to $\Delta^{1,4}$-3-ketones by DDQ, but in the presence of strong acid, dehydrogenation affords the $\Delta^{4,6}$-3-ketones. [122] In the event, treatment of 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol **59** with DDQ and toluene-*p*-sulfonic acid in methanol afforded the hexaene **64** in reasonable yield (58%) (Scheme 2.32).

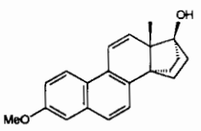
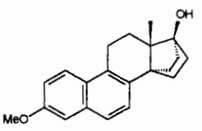


59 **64** **65**

Scheme 2.32 *Reagents and conditions*: **i**, DDQ, *p*-TsOH, MeOH, 25°C, 18h; Δ, 2h; **ii**, H_2, Pd-C, 25°C

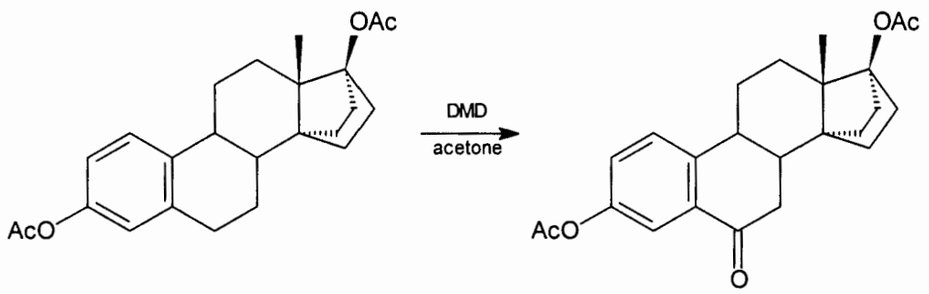
Selective hydrogenation of the Δ^{11}-bond of the hexaene **64** gave the pentaene **65**. The hexaene **64** and the pentaene **65** were readily identified from their ^{1}H NMR spectra, with the low field signals characteristic for ring B aromatic compounds clearly evident. [29] Table 2.9 summarises the important low field ^{1}H NMR data. These assignments were corroborated by the remaining spectral information and the analytical data.

Table 2.9: Selected ^{1}H NMR data for hexaene **64** and pentaene **65**

	Chemical shift δ/ppm (multiplicity, coupling constant *J*/Hz)	
Proton		
	64	**65**
1-H	δ 8.60 (d, *J* 9.3)	δ 7.92 (d, *J* 9.1)
2-H	δ 7.18 (dd, *J* 9.3 and 2.7)	δ 7.18 (dd, *J* 9.1 and 2.4)
4-H	δ 7.12 (d, *J* 2.7)	δ 7.12 (d, *J* 2.4)
6-H	δ 7.64 (d, *J* 8.3)	δ 7.57 (d, *J* 8.5)
7-H	δ 7.21 (d, *J* 8.3)	δ 7.20 (d, *J* 8.5)
11-H	δ 7.15 (d, *J* 9.8)	
12-H	δ 6.65 (d, *J* 9.8)	

The corresponding 3-hydroxy derivatives of the hexaene **64** and pentaene **65** (Scheme 2.32, 3-OH), previously synthesised by another route, [123] have been found to be biologically active. [124] While this reaction is of no use in the current synthesis, it does provide an alternative, more direct route to these compounds.

The introduction of the $\Delta^{9(11)}$-bond via the DMD C-9α-hydroxylation-dehydration reaction sequence [101, 102, 116] [successfully used in the unbridged series (Scheme 2.27)] was also investigated. DMD treatment of the 3,17β-diacetate **61** gave a complex mixture of products from which only 6-oxo-14,17α-ethano-3,17β-diacetate **66** could be isolated (16%). The molecular ion (*m/z* 396) indicated the addition of oxygen into the molecule, and the signal for 4-H in the ^{1}H NMR spectrum (δ 7.75, d, *J* 2.6 Hz) was diagnostic for the position of the new carbonyl group, as it is significantly deshielded by the 6-oxo functionality. [125] The remainder of the spectroscopic and analytical data were compatible with the proposed structure.



61 **66**

Scheme 2.33

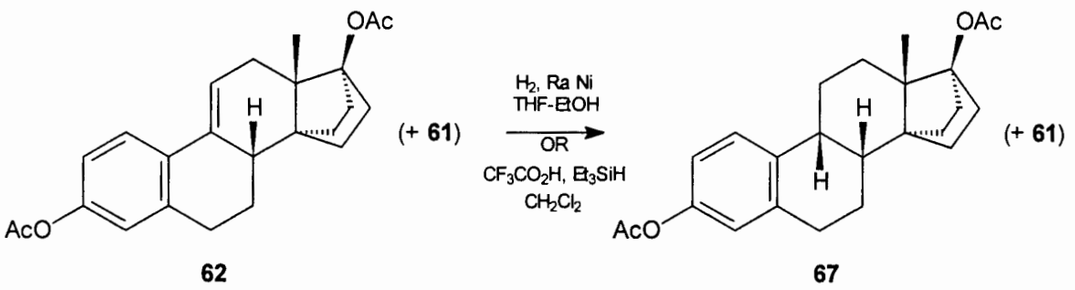
Presumably, the steric hindrance imposed by the 14α,17α-ethano bridge hinders reaction at the more reactive tertiary and benzylic C-9, allowing reaction at the less reactive secondary and benzylic C-6 to become a competitive process. [118, 119] It is assumed that the initially formed 6-hydroxy derivative is rapidly oxidised to the 6-ketone by DMD. [118]

Despite the foregoing success in introducing the desired $\Delta^{9(11)}$-bond into the 14,17-bridged system, it was recognised that the incomplete reaction and the resulting inseparable mixture of saturated and unsaturated compounds would necessitate subsequent reactions being conducted on this mixture.

Attempted catalytic hydrogenation (Pd-C, H_2) of the mixture of 3-methyl ethers **59** and **63**, gave an intractable mixture of products. ^{1}H NMR examination of this mixture indicated that there were at least three products present, thus rendering this reaction synthetically useless.

In contrast, catalytic hydrogenation of the mixture of 3,17β-diacetates **61** and **62** (H_2, Raney nickel) gave a separable mixture of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate **61** (52%) and 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diyl diacetate **67** (19%) (Scheme 2.34). If the 14α,17α-ethano 3,17β-diacetate **61** already present in the starting material (33%) is excluded, this ratio changes to 23:19 (instead of 52:19). Thus, the expectation that the 14α,17α-ethano bridge would affect the stereochemical course of the hydrogenation reaction was fulfilled with hydrogenation

occurring with approximately equal facility from either face of the molecule, providing access to the desired 14,17-bridged 9β-series.



62 **67**

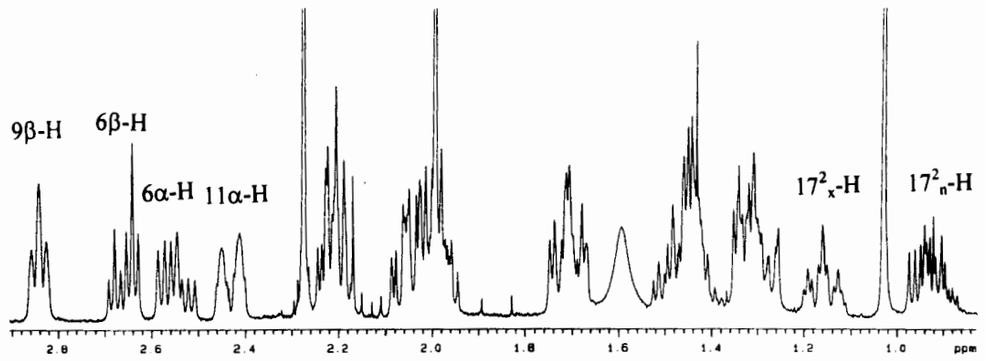
Scheme 2.34

Ionic hydrogenation was also attempted, in the hope that protonation of the intermediate carbocation [107] would occur selectively from the β-face, leading to an improved selectivity for the 9β-compound **67**. However, it is known that ionic hydrogenation tends to give products with the more stable, natural *trans-anti-trans* configuration in unsubstituted estratetraenes [107] and this could also occur in the present series, thereby reducing the amount of 9β-product being formed.

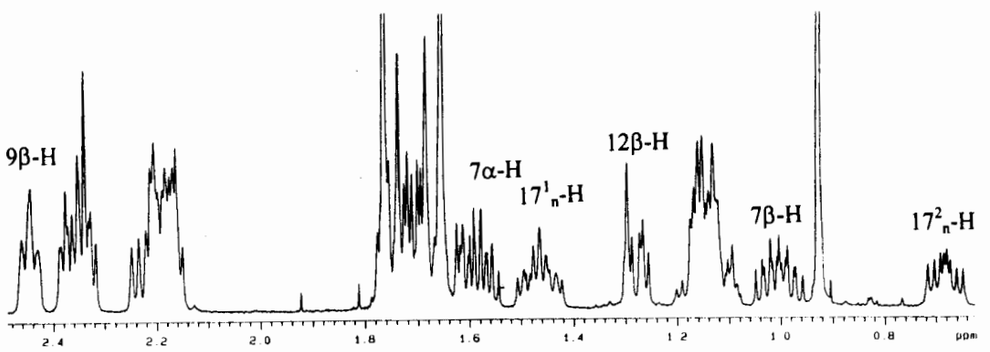
The reaction proceeded extremely slowly (7 days) to give the same two products in an 5:1 ratio. If the 14α,17α-ethano 3,17β-diacetate **61** already present in the starting material (33%) is excluded, as before, this ratio changes to 2:1. Thus this reaction appears to be more α-face selective than normal hydrogenation, indicating that the preference for forming the thermodynamically more stable product dominates over steric considerations.

14,17α-Ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate **61** was identified by comparison with authentic material made previously. Although it was considered unlikely that any other product could have resulted from this reaction sequence, the other isomer, 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diyl diacetate **67** was thoroughly examined by spectroscopic techniques in order to ensure that the assigned structure was correct, and to obtain information about the conformation of the molecule in solution. Figure 2.28 shows the high-field region of the ^{1}H NMR spectrum of **67** in deuteriobenzene (C_6D_6) and

deuteriochloroform ($CDCl_3$). Some of the assignments have been tabulated (Table 2.10). Figure 2.29 shows a portion of the COSY spectrum of **67** (C_6D_6).



(a)



(b)

Figure 2.28: ^1H NMR spectrum of 14,17α-ethano-9β-estra-1,3,5(10)-trien-3,17β-diyl diacetate **67** (a) $CDCl_3$ and (b) C_6D_6

Table 2.10: Selected proton signals for 14,17α-ethano-9β-estra-1,3,5(10)-trien-3,17β-diyl diacetate **67** in deuteriochloroform and deuteriobenzene

	Chemical shift δ/ppm (multiplicity, coupling constant *J*/Hz)	
Proton	$CDCl_3$	C_6D_6
1-H	δ 7.31 (d, *J* 8.5)	δ 7.07 (d, *J* 8.3)
2-H	δ 6.89 (dd, *J* 8.5 and 2.5)	δ 6.93 (dd, *J* 8.3 and 2.3)
4-H	δ 6.82 (d, *J* 2.5)	δ 6.88 (d, *J* 2.3)
6α-H	δ 2.55 (ddd, *J* 15, 11 and 5.6)	δ 2.20 (m, obsc.)
6β-H	δ 2.66 (dt, *J* 15 and 2 x 5.2)	δ 2.35 (m, obsc.)
7-H_2	δ 1.30, 2.00 (both m, obsc.)	δ 1.00 (m), 1.58 (m, obsc.)
8β-H	δ 2.22 (m, obsc.)	δ 1.72 (m, obsc.)
9β-H	δ 2.84 (br t, *J* 6.2)	δ 2.44 (br t, *J* 6.7)
11α-H	δ 2.44 (br dq, *J* 15)	δ 2.18 (m, obsc.)
11β-H	δ 2.00 (m, obsc.)	δ 1.72 (m, obsc.)
12α-H	δ 1.30 (m, obsc.)	δ 1.66 (m, obsc.)
12β-H	δ 1.70 (m, obsc.)	δ 1.28 (dt, *J* 12.6 and 2 x 4.1, obsc.)
17^2_x-H	δ 1.16 (dt, *J* 13 and 2 x 3.5)	δ 1.15 (m, obsc.)
17^2_n-H	δ 0.94 (ddd, *J* 13, 9.8 and 5.2, obsc.)	δ 0.68 (ddd, *J* 12.6, 9.9 and 5.1)

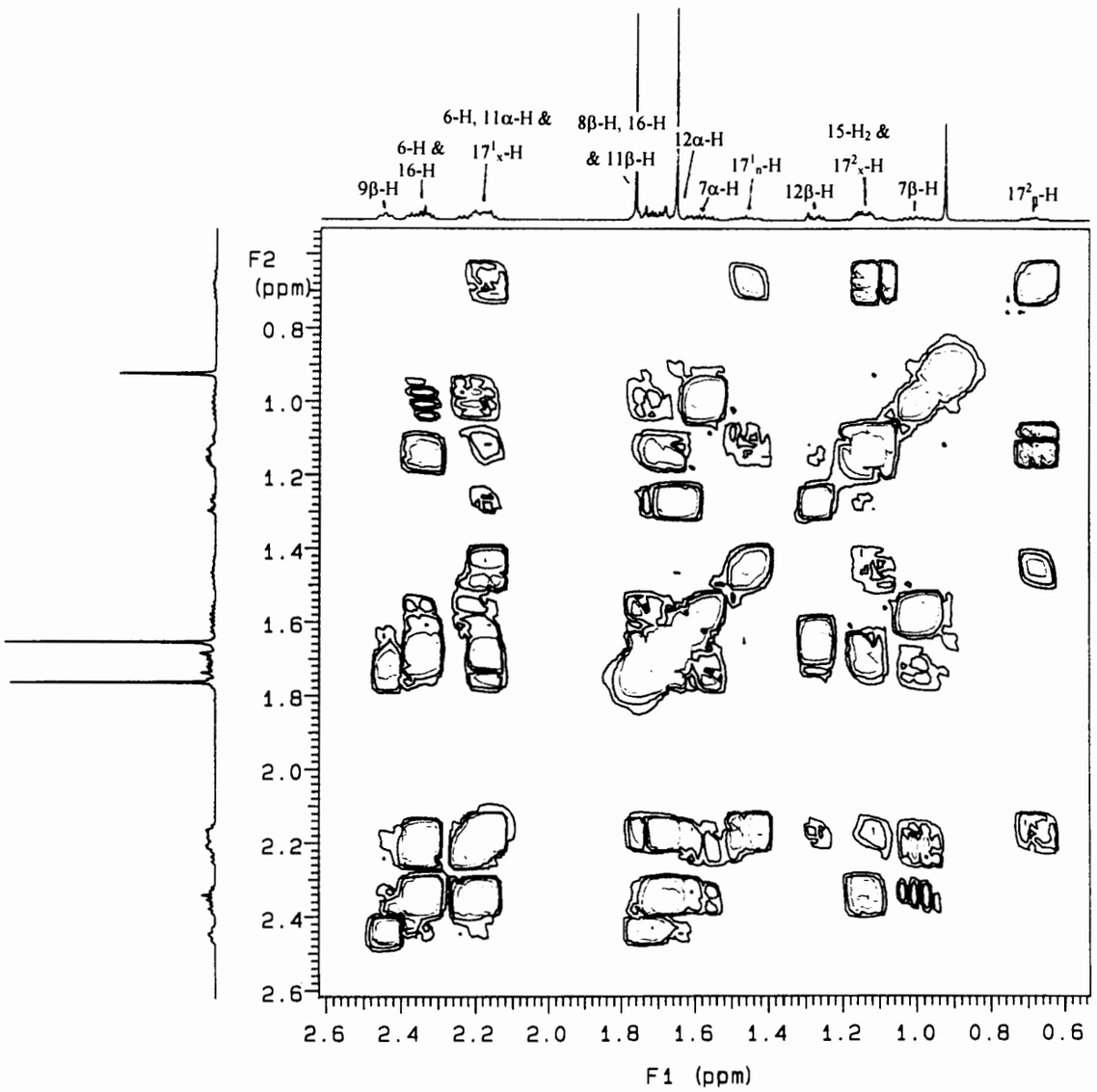


Figure 2.29: High field region of COSY spectrum of 14,17α-ethano-9β-estra-1,3,5(10)-trien-3,17β-diyl diacetate **67**

Support for the assigned stereochemistry at C-9 was obtained from a NOE difference experiment (Figure 2.30). Figure 2.31 shows the observed NOE enhancements. The 9β-configuration was indicated by the enhancement of the signal for 12α-H (δ 1.64-1.68; *ca* 2%) observed on irradiation of 1-H (δ 7.07) (Figure 2.31). Also observed was an

enhancement of the signal for 11α-H (δ 2.2; 7%). Irradiation of the 13β-methyl group enhanced the signals for 11β-H and 12β-H, confirming the identity of 11α-H and 12α-H from the observed crosspeaks in the COSY spectrum (Figure 2.29)

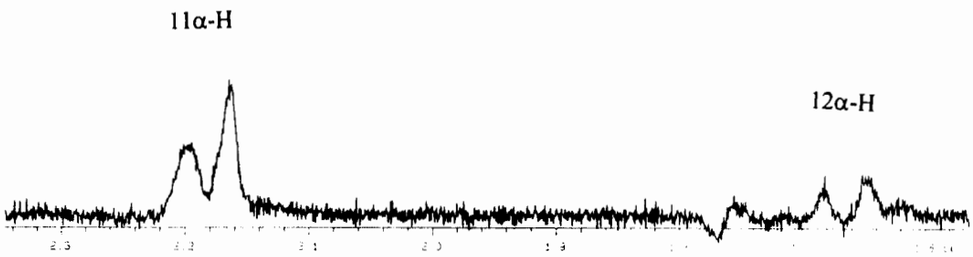


Figure 2.30: NOE difference spectrum of 14,17α-ethano-9β-estra-1,3,5(10)-trien-3,17β-diyl diacetate **67**, irradiation of 1-H (δ 7.07, C_6D_6).

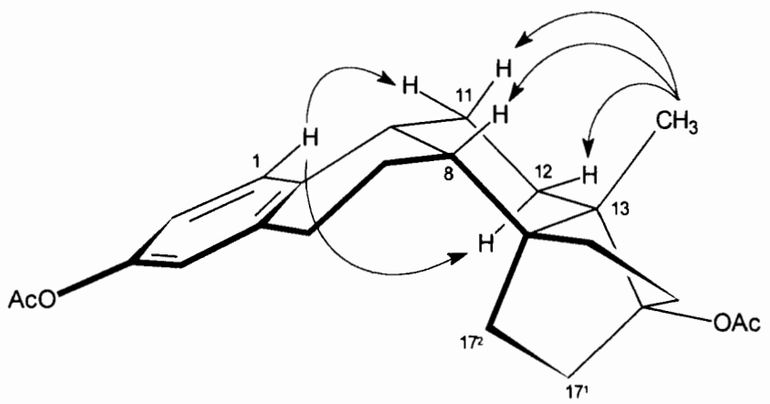
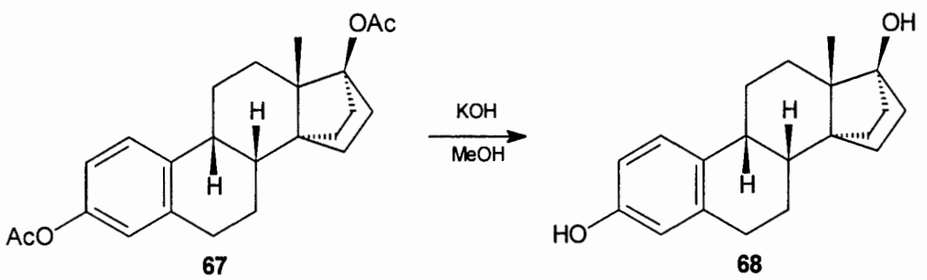


Figure 2.31: Perspective view of 14,17α-ethano-9β-estra-1,3,5(10)-trien-3,17β-diyl diacetate **67**, indicating observed NOE enhancements

Further support for this 'folded' conformation was obtained from the signals for 17^2-H_2, which both appear to be quite significantly shielded by the aromatic ring. In the corresponding compound in the natural series, the corresponding signals, although not conclusively identified, resonate between δ 1.2 and δ 2.0. This shift showed a significant solvent dependence, with a different shielding being observed in deuteriobenzene than deuteriochloroform, in $CDCl_3$: 17^2_x (δ 1.16, dt, *J* 13 and 2 x 3.5 Hz), 17^2_n (0.94, ddd, *J* 13,

9.8 and 5.2 Hz), in C_6D_6: 17^2_x (δ 1.15, m, obsc.), 17^2_n (0.68, ddd, *J* 12.6, 9.9 and 5.1 Hz), this is possibly due to the molecule adopting slightly different conformations in the two solvents. A similar shielding of a 14α-substituent by the aromatic ring of a 9β-steroid has been observed in 3-methoxy-14α-methyl-9β-estra-1,3,5(10)-trienes. [29]

Alkaline hydrolysis of the 3,17β-diacetate **67** afforded 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diol **68** (91%) which was subjected to biological evaluation (Scheme 2.35).



67 **68**

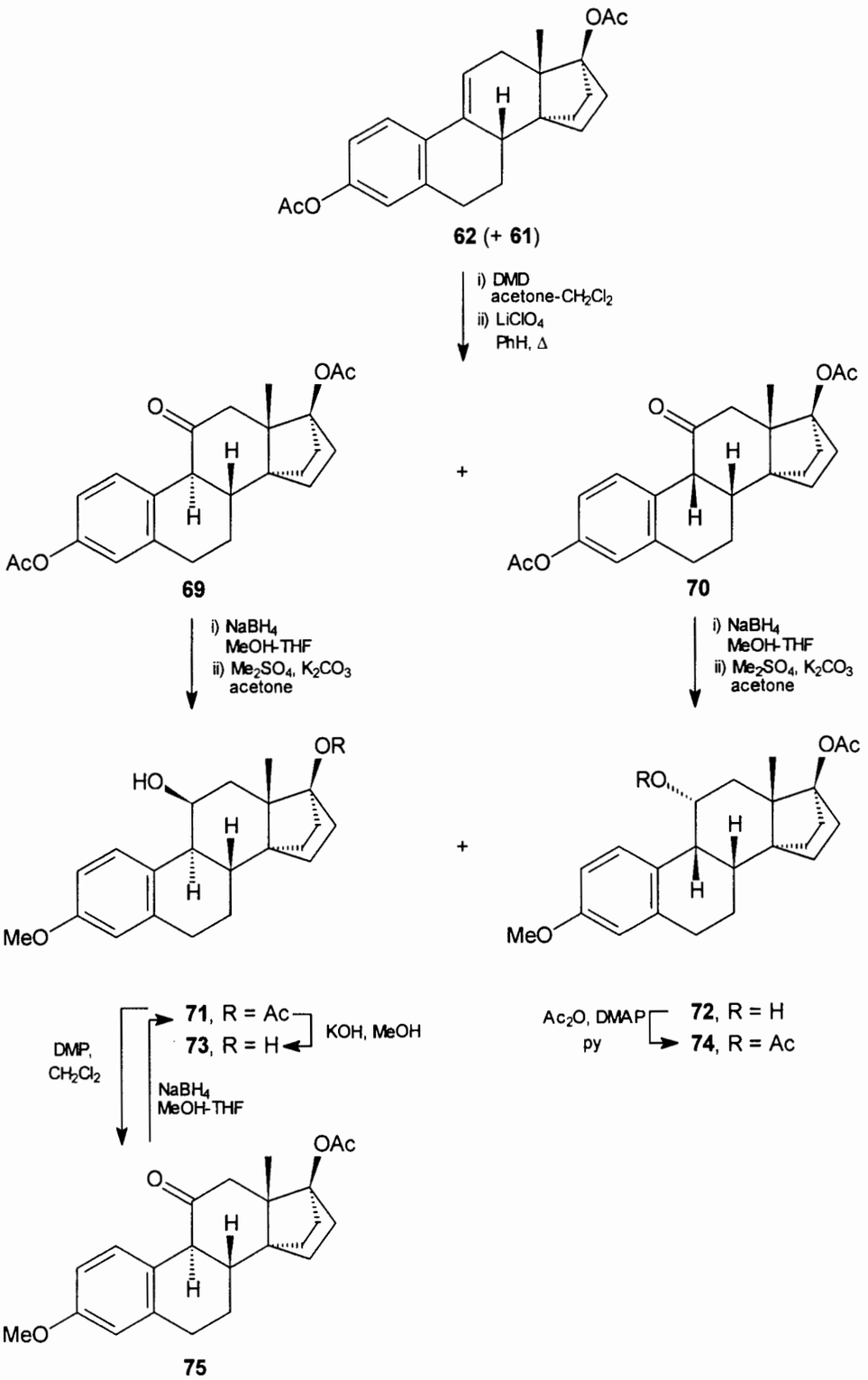
Scheme 2.35

In conjunction with this successful synthesis of 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diol **68**, other possible routes to this target, as mentioned in the introduction to this section (Scheme 2.23), were explored and the results of this investigation will be presented in the next section.

2.3.3 Further reactions of 14α,17α-ethano $\Delta^{9(11)}$-derivatives 61 and 63

The two other possible routes towards the 9β-series of compounds previously discussed (Scheme 2.23, p. 55) are the epoxidation-rearrangement sequence (**g** to **h** or **i**) successfully utilised in the unbridged series (Section 2.3.1) and the hydroboration-oxidation-equilibration sequence (**g** to **h** to **i**). The first route is dependent on achieving an α-selective epoxidation, which appears unlikely in the bridged series, in the light of the hydrogenation experiment described previously. Similarly, the hydroboration-oxidation reaction sequence was not expected to provide a synthetically useful access to the 9β-series, for the reasons mentioned in the introduction (p. 55). Despite this, it was decided to explore these reaction sequences, both to investigate the possibility of synthesising 9β-compounds by these routes, albeit in small amounts, and to obtain access to 11-functionalised estradiol derivatives. The latter are of interest as several such compounds display enhanced hormonal activities. [54, 126]

The results obtained for the epoxidation-rearrangement reaction sequence will be presented first. The choice of protecting groups (acetate) and reagents (DMD, $LiClO_4$) for accomplishing this transformation was influenced by the experience gained from the unbridged series (Scheme 2.28). Although a mixture of products **61** + **62** was used for this reaction (as before), only the $\Delta^{9(11)}$-compound **62** has been displayed for convenience.


OAc
AcO
62 (+ 61)
i) DMD
acetone-CH2Cl2
ii) LiClO4
PhH, Δ
69
70
i) NaBH4
MeOH-THF
ii) Me2SO4, K2CO3
acetone
OR
HO
MeO
RO
71, R = Ac
73, R = H
KOH, MeOH
DMP,
CH2Cl2
NaBH4
MeOH-THF
Ac2O, DMAP
py
72, R = H
74, R = Ac
75

Scheme 2.36

Epoxidation of the mixture of 3,17β-diacetates **61** + **62** with DMD followed by a lithium perchlorate catalysed 1,2-hydride shift (as in the unbridged series) gave the 3,17β-diacetate **61** (33%) and a mixture of the epimeric 11-ketones **69** and **70** (46%) (Scheme 2.36). Recrystallisation afforded pure 3,17β-diacetoxy-14,17α-ethanoestra-1,3,5(10)-trien-11-one **69**. The 11-ketone **69** was characterised by a strong absorption in the infrared spectrum at ν_{max} 1732 cm^{-1}, along with the expected molecular ion and microanalytical data. The configuration at C-9 was assigned from the ^1H NMR in which the signal for 9α-H (δ 3.89, d, *J* 12.8 Hz) indicates a 9α-configuration. This was confirmed by subsequent experiments.

In order to conserve material, the crude mixture of 11-ketones **69** and **70** was treated with sodium borohydride in methanol, followed by chemoselective 3-O-methylation to afford a separable mixture of 11β-hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β-yl acetate **71** (56%) and 11α-hydroxy-3-methoxy-14,17α-ethano-9β-estra-1,3,5(10)-triene-17β-yl acetate **72** (11%).

The major product, 11β-hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-17β-yl acetate **71** was readily identified from spectral data. The signal for the 13β-Me group (δ 1.19) is deshielded by the 1,3-diaxial relationship with 11β-OH. The signal for 9α-H (δ 2.8) is unfortunately masked by the signal for 6-H_2, but that of 11α-H (δ 4.75, q, *J* 3 x 3.2 Hz) clearly indicated the equatorial orientation of this proton. A small-scale deacetylation reaction (KOH, MeOH) gave the 11β,17β-diol **73** which displayed similar spectral characteristics to the precursor 17β-acetate **71**. For this derivative it proved possible to unravel the signal for 9α-H (δ 2.89, dd, *J* 12 and 3.3 Hz), providing further confirmation of the stereochemistry at C-9 and C-11.

The minor isomer, 11α-hydroxy-3-methoxy-14,17α-ethano-9β-estra-1,3,5(10)-triene-17β-yl acetate **72** was readily identified as an 11α-hydroxylated product by ^1H NMR spectroscopy, from the deshielding of 1-H (δ 7.67, d, *J* 8.3 Hz). The configuration at C-9 was inferred from the signal for that proton (δ 3.11, dd, *J* 7.3 and 5.3 Hz).

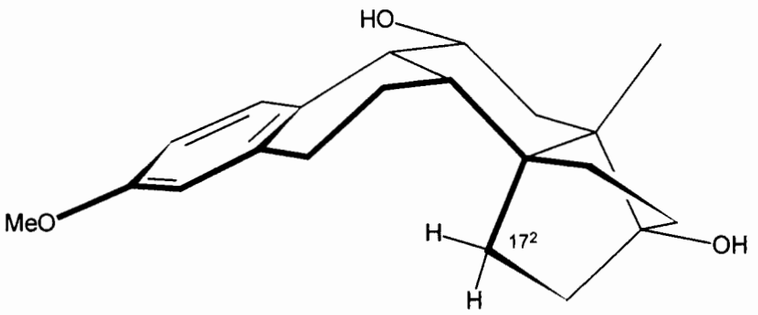


Figure 2.32: Perspective drawing of 11α-hydroxy-3-methoxy-14,17α-ethano-9β-estra-1,3,5(10)-triene-17β-yl acetate **72**, indicating the folded conformation

Further support for the assigned stereochemistry at C-9 was obtained from the high-field region of the ^{1}H NMR spectrum, where a one proton multiplet (δ 0.94, m) was observed (for 17^2_n-H), unlike in the natural series. This shielding of a 14α-substituent appears to be characteristic of 9β-estratrienes in the folded conformation depicted (Figure 2.32). [29]

This assignment was subsequently confirmed by the synthesis of 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-11α,17β-diol **76** (p. 84), which displayed substantially different coupling constants in the ^{1}H NMR spectrum, excluding the possibility that reduction of the 9α*H*-11-ketone **69** could have afforded a 9α*H*-11α-hydroxy compound as a minor product. The important ^{1}H NMR signals of selected 11-hydroxylated derivatives have been tabulated for comparison purposes (Table 2.12, p. 86).

As the 11α-hydroxy-14,17α-ethano-9β-17β-acetate **72** was not crystalline, the corresponding 11α,17β-diacetate **74** was synthesised (74%) in an attempt to obtain a suitable derivative for characterisation purposes. This material was also non-crystalline, and was characterised by spectra and an accurate mass determination, which fully supported the assigned structure.

In order to exclude the possibility that the 11-ketone **69** could undergo epimerisation at C-9 prior to reduction, the 9α*H*-11-ketone **69** was stirred with hydrochloric acid in methanol [54] for 24h. No evidence of equilibration was observed, indicating that the 11α-alcohol **72**

originates from reduction of the 9β*H*-11-ketone **70**. Base-mediated equilibration was not feasible on this substrate due to the extremely base-sensitive 3-acetoxy group.

Oxidation of the 11β-alcohol **71** (DMP, CH_2Cl_2) [72] gave the 11-ketone **75** (68%). Reduction of a portion of the crude product prior to any purification gave the starting 11β-alcohol **71**, with no other products either observed (TLC) or isolated. This confirms that epimerisation at C-9 prior to reduction of the 11-ketone does not occur. Hence the source of the 11α-alcohol **72** must be the corresponding 9β*H*-11-ketone **70**, present as an unidentified minor product of the epoxidation-rearrangement sequence (Scheme 2.36).

The 11-ketone, **75**, displayed all the expected analytical and spectral characteristics, similar to the previously synthesised 11-oxo-3,17β-diacetate **69**. Figure 2.33 shows the high-field region of the ^{1}H NMR spectrum, and some of the assignments are tabulated (Table 2.11). The signal for 9α-H (δ 3.88, d, *J* 12.2 Hz) had a similar coupling constant to that previously observed, and was taken as evidence of the 9α-configuration. In order to confirm this assignment, and those made previously, a NOE difference experiment was conducted (Figure 2.34).

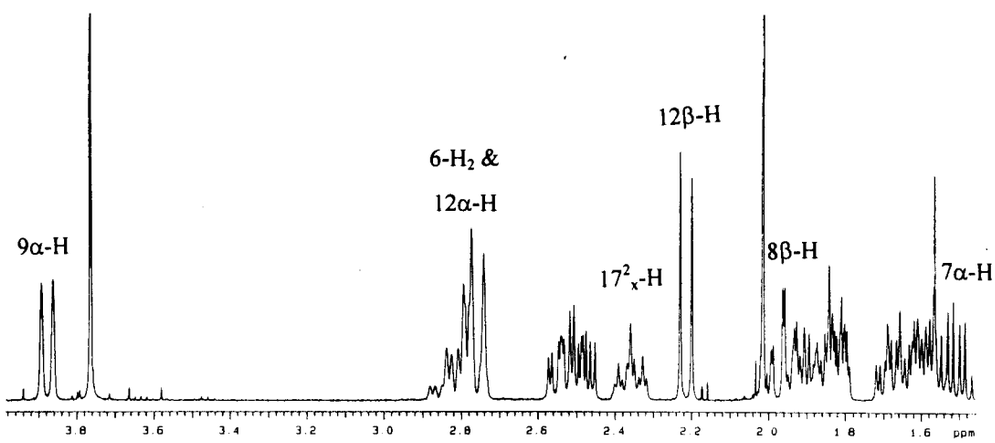


Figure 2.33: ^{1}H NMR spectrum of 3-methoxy-11-oxo-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate **75**

Table 2.11: Key signals in the ^{1}H NMR spectrum of 3-methoxy-11-oxo-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate **75**

δ / ppm	Int.	Mult.	*J* / Hz	Assignment
2.22	1H	d	12.0	12β-H
2.36	1H	tt	2 x 12.7 and 2 x 3.7	17^2_x-H
2.76	1H	dd	12 and 0.8	12α-H
3.88	1H	d	12.2	9α-H

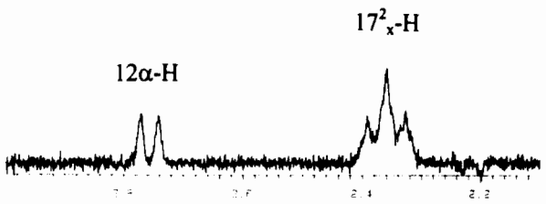


Figure 2.34: NOE difference spectrum of 14α,17α-ethano 11-ketone **75** (irradiation of 9α-H, δ 3.88)

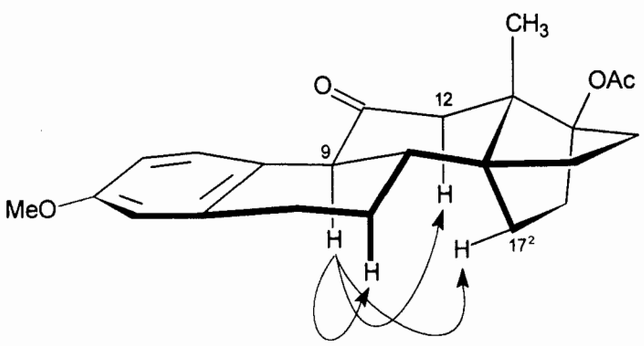


Figure 2.35: Perspective view of 14α,17α-ethano 11-ketone **75** indicating observed NOE enhancements

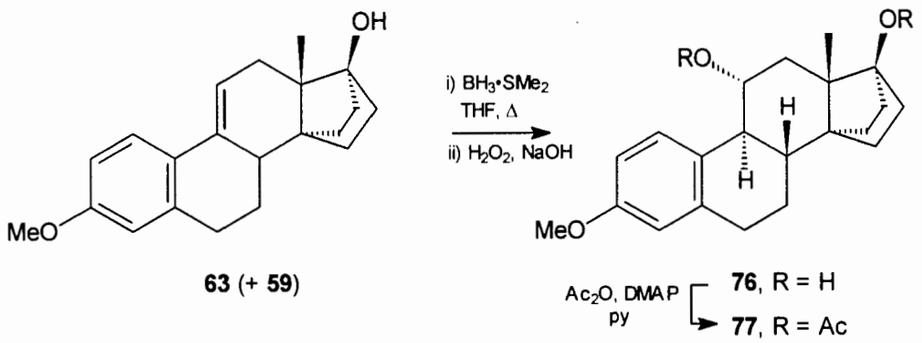
Irradiating the signal for 9α-H (δ 3.88) enhanced the signals for 7α-H (δ 1.52, *ca* 2%), 17^2_x-H (δ 2.36, 13%) and 12α-H (δ 2.76, 4%), thus confirming this assignment, and hence also the remainder of the assignments (Figure 2.35).

Thus, conclusive proof of the 9α-configuration of the 11-ketone **75** has been obtained, confirming previous assignments. Additionally, from the assignment of 17^2_x-H from NOE difference spectroscopy, it was possible to assign the ^{13}C NMR signals of the two ethano bridges (C-15, C-16 and C-17^1, C-17^2). These have been used to help assign the carbon resonances of all the 14α,17α-ethano bridged compounds reported in this thesis, as in most cases it is impossible to differentiate between these signals.

In conclusion, it has been demonstrated that the presence of the 14α,17α-ethano bridge significantly diminishes the α-face stereoselectivity of epoxidation of the $\Delta^{9(11)}$-bond, thus reducing the synthetic utility of this approach to 9β-derivatives of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol. However, it does provide efficient access to the 11-ketones **69** and **71**, which are versatile precursors to 11-functionalised derivatives. [105, 127]

Hydroboration-oxidation of the $\Delta^{9(11)}$-bond was also investigated. For this reaction sequence the base-labile 3-acetate was inappropriate, so the mixture of 3-methyl ethers **59** and **63** was used. Although this route was not expected to provide a synthetically useful entry into the 9β-series, it was hoped that the 14α,17α-ethano bridge would influence the stereoselectivity of the hydroboration reaction, similarly to the hydrogenation and epoxidation reactions previously described. Once again, for convenience, only the $\Delta^{9(11)}$-olefin constituent, **63**, of the starting material has been displayed.

Hydroboration-oxidation of the $\Delta^{9(11)}$-compound **63** (contaminated with the saturated analogue **59**) gave compound **59** (35%) followed by the 11α-alcohol **76** (31%) (Scheme 2.37). From both the ^{1}H NMR data and TLC, no evidence of any isomer was observed. This result is similar to that obtained for the hydroboration/oxidation of 17β-*t*-butyloxy-14α-methyl-3-methoxyestra-1,3,5(10),9(11)-tetraene. [55] Evidently, the presence of a 14α-substituent does not significantly affect the selectivity of hydroboration-oxidation, unlike hydrogenation and epoxidation reactions.



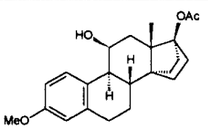
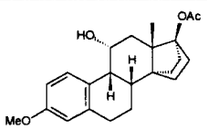
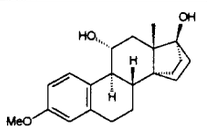
Scheme 2.37

The configuration at both C-9 and C-11 was assigned by comparison with the previously synthesised 11-alcohols, **71** and **72** (Table 2.12). The presence of an 11α-hydroxy group was indicated by the deshielding of the signal for 1-H (δ 7.88, d, *J* 8.7 Hz), while the signal for 9α-H (δ 2.48, t, *J* 2 x 10 Hz), with two large couplings, indicative of two anti-periplanar relationships (with 8β-H and 11β-H) confirmed this.

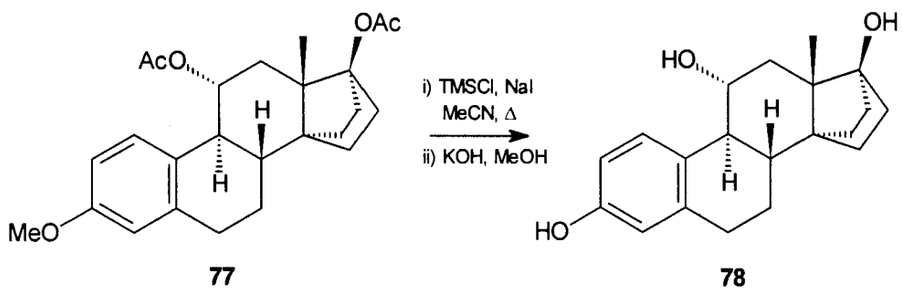
As the 11α,17β-diol **76** was not crystalline, it was characterised as the 11α,17β-diacetate **77** (74% yield for the conversion). The 11α,17β-diacetate **77** displayed similar characteristics to the precursor **76**. In the case of the 11α,17β-diacetate **77**, it proved impossible to obtain the molecular ion (m/z 412) in the mass spectrum. A primary fragmentation ion (m/z 352) corresponding to the loss of acetic acid was clearly evident.

For comparison, key ^{1}H NMR signals for representative members of all the 11-oxygenated 14α,17α-ethanoestratriene derivatives synthesised have been tabulated (Table 2.12).

Table 2.12: ^{1}H NMR data for selected 11ξ-hydroxy 14α,17α-ethano bridged compounds **71**, **72** and **76**

Proton(s)	Chemical shift δ/ppm (multiplicity, coupling constant *J*/Hz)		
			
	71	**72**	**76**
13β-Me	δ 1.19 (s)	δ 1.09 (s)	δ 0.89 (s)
9-H	α: δ 2.77 (m)	β: δ 3.11 (dd, *J* 7.3 and 5.3)	α: δ 2.48 (t, *J* 2 x 10)
11-H	α, δ 4.75 (q, *J* 3 x 3.2)	β, δ 4.57 (dt, *J* 8.8 and 2 x 5.3)	β, δ 4.20 (td, *J* 2 x 10 and 5.8)
1-H	δ 7.23 (d, *J* 8.5)	δ 7.67 (d, *J* 8.3)	δ 7.88 (d, *J* 8.7)

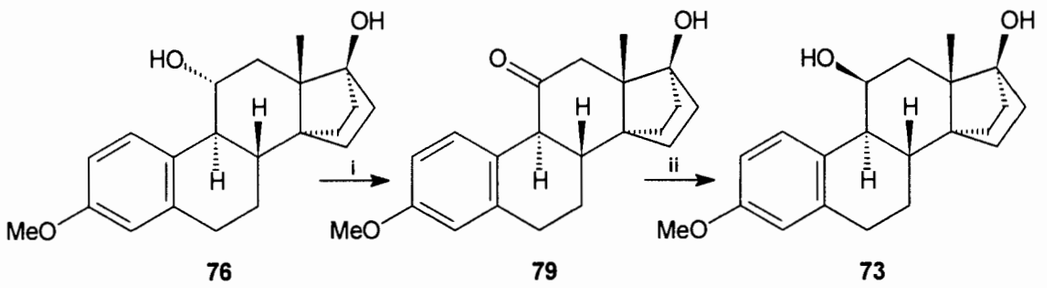
Demethylation, [128] followed by deacetylation of the 3-methoxy-11α,17β-diacetate **77** afforded the 3,11α,17β-triol **78** (65%) (Scheme 2.38) which was subjected to biological evaluation.



77 **78**

Scheme 2.38

Swern oxidation [70] of the 11α-alcohol **76** afforded the 11-ketone **79** (58%) (Scheme 2.39). The structure was readily assigned from a comparison of the ^{1}H NMR spectrum with that of the previously synthesised 11-oxo 17β-acetate **75**.



76 **79** **73**

Scheme 2.39 *Reagents and conditions*: **i**, a) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; b) Et_3N, -78°C→25°C; **ii**, LAH, THF, 25°C

Reduction of the 11-ketone **79** (LAH, THF) gave the 11β-alcohol **73** which was identical to that synthesised previously, providing conclusive proof for the assigned stereochemistry at C-9 and C-11. As expected, the 11-ketone **79** was recovered unchanged after acid-mediated equilibration. [54] However, attempted base-mediated equilibration [54, 100] gave an intractable mixture of products which could not be identified. Refinement of the reaction conditions might provide a more interpretable result, but in the light of the acid-mediated equilibration reaction this was not investigated.

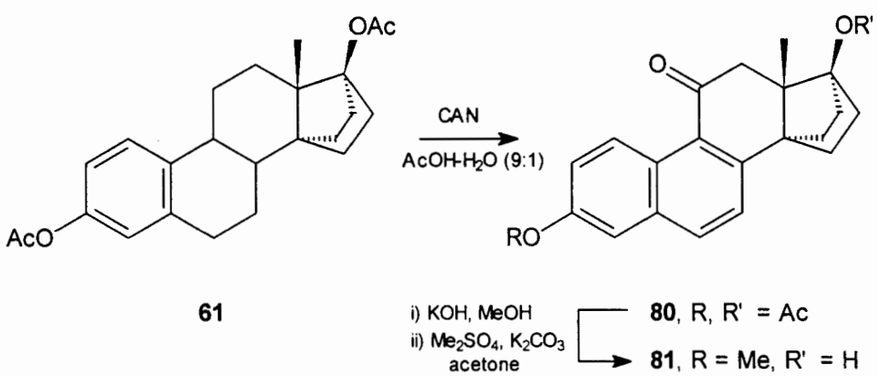
In conclusion, a number of interesting ring C oxygenated 14,17α-ethano bridged estradiol derivatives have been synthesised. Although access to the desired 9β-series is achieved by the methods described, this is not a synthetically viable route. The 11-ketones **69**, **75** and **79** are potential precursors to 11-alkylated 14,17α-ethanoestradiol derivatives following the procedure established for the unbridged series [127] (Grignard or alkyllithium addition to the 11-ketone followed by ionic hydrogenation of the resulting tertiary alcohol).

2.3.4 Other methods of ring C functionalisation

An alternative method of introducing ring C functionality to be investigated was cerium(IV) ammonium nitrate (ceric ammonium nitrate, CAN) oxidation, as it has been reported that CAN treatment of estrone 3-acetate gives the corresponding 9α,11β-diol 11-nitrate ester. [129] This intermediate has been used in the preparation of a number of estradiol analogues with 'remarkable' biological activity. [130]

Of more interest to this work was the reported conversion of the 9α,11β-diol 11-nitrate ester into the 9α,11α-epoxide. [131] As has been demonstrated, this epoxide can be converted into the 9β*H*-11-ketone. [100] As direct epoxidation-rearrangement of the 14α,17α-ethano $\Delta^{9(11)}$-compound **62** did not provide efficient access to the desired 9β*H*-11-ketone **70**, this indirect approach was investigated.

CAN oxidation of the 3,17β-diacetate **61** unexpectedly gave 11-oxo-14,17α-ethanoestra-1,3,5(10),6,8-pentaene-3,17β-diyl diacetate **80** instead of the anticipated 9α,11β-diol 11-nitrate ester (Scheme 2.40). Subsequently, independent confirmation of this result was obtained from a publication describing this transformation. [123]



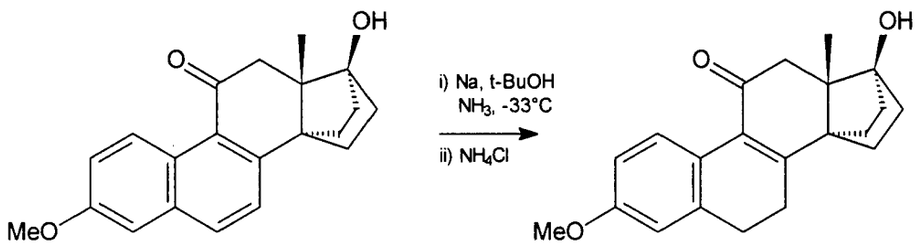
Scheme 2.40

The ^{1}H NMR spectrum of **80** showed all the expected signals for the aromatic system, and these are summarised in Table 2.13 along with the ^{1}H NMR signals for other, related compounds. The significant deshielding observed for 1-H is due to the planarity of the

11-ketone and the aromatic system forcing this proton into the deshielding region of the 11-ketone, and has been observed for other 11-oxo equilenin derivatives. [132]

It has been reported [132-134] that Birch reduction of 11-oxoequilenin systems gives the corresponding 11-oxoestra-1,3,5(10),8-tetraenes. Further reduction has been reported to give either a poor yield of the 11α-hydroxy-8β,9α-estratriene [132] or the 11-oxo-8β,9α-triene. [135]

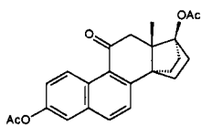
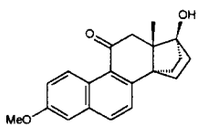
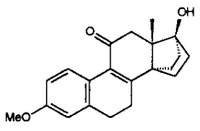
For the purpose of performing a comparable reduction on the current system, the 3-acetoxy group of **80** was replaced by a 3-methyl ether using standard methodology, affording **81**. The ^{1}H and ^{13}C NMR spectra of this compound, **81**, were assigned with by standard 2-D NMR spectroscopic techniques. Treatment of the 11-ketone **81** under Birch reduction conditions (sodium, ammonia, t-BuOH) gave the Δ^{8} 11-ketone **82** in variable yields (68% at best) (Scheme 2.41). This reaction remained capricious despite all attempts at optimisation, with the yield fluctuating substantially. The Δ^{8} 11-ketone **82** was readily identified from spectral information, with the loss of the signals for 6-H and 7-H from the aromatic region of the ^{1}H NMR spectrum clearly indicating that saturation of the olefinic bond between C-6 and C-7 had occurred.



81 **82**

Scheme 2.41

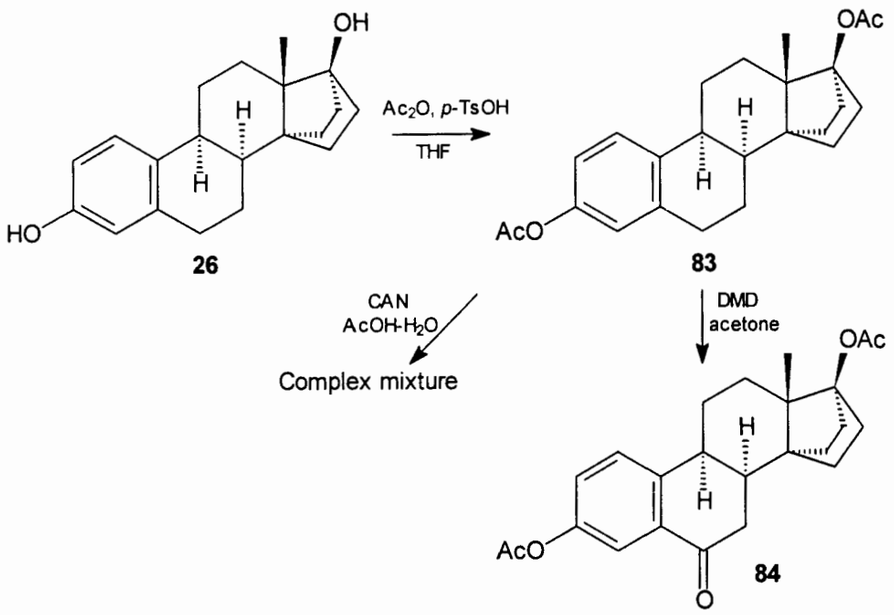
Table 2.13: Selected ^{1}H NMR signals for 11-oxo-14,17α-ethano derivatives **80**, **81** and **82**

	Chemical shift δ/ppm (multiplicity, coupling constant *J*/Hz)		
Proton			
	80	**81**	**82**
1-H	δ 9.40 (d, *J* 9.5)	δ 9.30 (d, *J* 9.6)	δ 7.97 (d, *J* 8.6)
2-H	δ 7.36 (dd, *J* 9.5 and 2.5)	δ 7.29 (dd, *J* 9.6 and 2.9)	δ 6.78 (dd, *J* 8.6 and 2.7)
4-H	δ 7.55 (d, *J* 2.5)	δ 7.12 (d, *J* 2.9)	δ 6.70 (d, *J* 2.7)
6-H	δ 7.95 (d, *J* 8.5)	δ 7.90 (d, *J* 8.3)	
7-H	δ 7.32 (d, *J* 8.5)	δ 7.26 (d, *J* 8.3 Hz)	
12α-H	δ 3.20 (dd, *J* 18 and 1.2)	δ 2.98 (dd, *J* 18 and 1.2)	δ 2.74 (dd, *J* 17 and 1.2)
12β-H	δ 2.61 (d, *J* 18)	δ 2.55 (d, *J* 18)	δ 2.40 (d, *J* 17)

Further reduction of the Δ^8 11-ketone **82** (lithium/ammonia or hydrogenation) failed to provide any synthetically useful products, and this approach was discontinued.

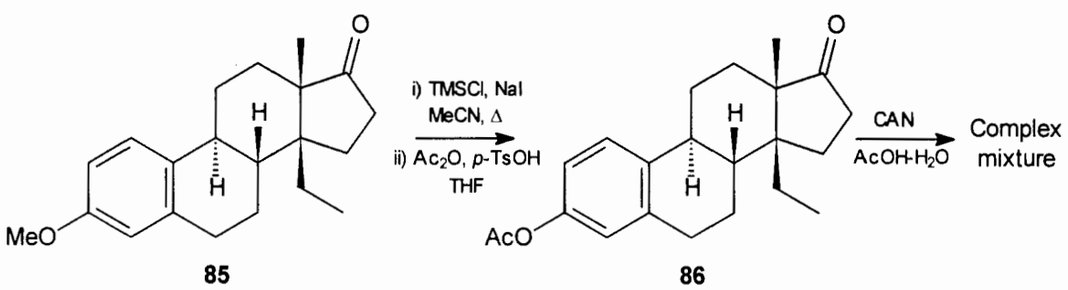
In an attempt to explore the general applicability of this unusual oxidation reaction, two other 14-functionalised analogues were prepared. 14,17α-Ethano-8α-estra-1,3,5(10)-triene-3,17β-diyl diacetate **83** was readily synthesised from the 3,17β-diol **26**. CAN oxidation of the 3,17β-diacetate **83** afforded a complex mixture of products (Scheme 2.42).

Interestingly, DMD treatment of the 3,17β-diacetate **83** afforded a moderate yield (50%) of the 6-ketone **84**, readily identified from ^{1}H NMR and ^{13}C NMR data; key signals were those for 4-H (δ 7.69, d *J* 2.5 Hz) and C-6 (δ 197.4). This result is comparable with that observed in the natural series (see p. 70); however, the yield is substantially better.



Scheme 2.42

3-Acetoxy-14β-ethylestra-1,3,5(10)-trien-17-one **86** was synthesised from 14β-ethyl-3-methoxyestra-1,3,5(10)-triene-17-one **85**. [136] Demethylation with trimethylsilyl chloride-sodium iodide [128] followed by acid-catalysed acetylation gave the desired product in good overall yield (70%) (Scheme 2.43). CAN oxidation of this material once again failed to give an interpretable result, with complex mixtures of products invariably being isolated.

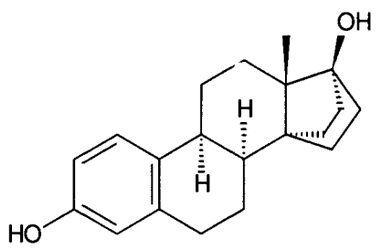


Scheme 2.43

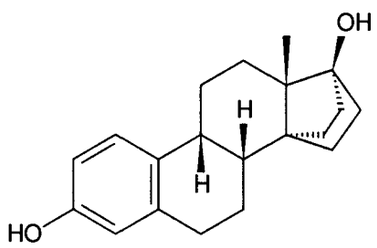
Thus, the only conclusion drawn from this preliminary study is that the presence of an alkyl substituent at C-14 prevents the reaction from proceeding as in 14-unsubstituted compounds, possibly due to steric hindrance.

2.4 Conclusions

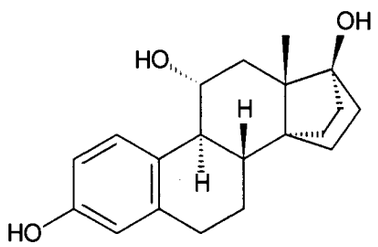
In conclusion, the primary objectives of this section of the project, the synthesis of skeletally modified 14,17α-ethanoestradiol analogues have been largely met. Both 14,17α-ethano-8α-estra-1,3,5(10)-triene-3,17β-diol **26** and 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diol **68** have been successfully synthesised. The inability to induce diene formation in the 13α-series prevented further work towards the synthesis of 14,17α-ethano-13α-estra-1,3,5(10)-triene-3,17β-diol being performed. Figure 2.36 summarises all the estradiol analogues synthesised in this section along with their competitive binding affinities for the estradiol receptor, expressed as a competition factor (see Appendix 1 for details). [24]



26, CF 2.2



68, CF 7.9



78, CF 273

Figure 2.36: Estradiol analogues synthesised, along with their competition factors

Thus, the 8α-derivative displayed significant receptor binding affinity, while inversion at C-9 led to a fairly substantial reduction in competitive binding affinity. This will be discussed in more detail in Chapter 4. The introduction of an 11α-hydroxy group led to a

complete loss of binding affinity, as has been observed in the unbridged series, [26] confirming the hydrophobic nature of the receptor in that region.

The route developed for the synthesis of 8α-analogue **26** allows for the preparation of a number of other analogues of 8α-estradiol, and some of the precursors to these compounds have been synthesised.

Although the route developed for the synthesis of the 9β-analogue **68** is less amenable towards the preparation of a large variety of analogues of 9β-estradiol it can be applied to any 14α-functionalised estradiol analogue. Efficient access to C-11 functionalised 14α,17α-ethanoestradiol analogues has also been achieved.

Future work directed towards the synthesis of 9β-steroids should be focused on developing a total synthesis route towards a 9β-estrone derivative for further modification. The inversion methodology developed in both the 14,17-bridged as well as in the unbridged series is rather laborious and low yielding.

Two potential precursors identified in this context are 14β-hydroxy-3-methoxy-9β-estra-1,3,5(10)-trien-17-one, available from the hydrogenation of 14β-hydroxy-3-methoxyestra-1,3,5(10),8-tetraen-17-one [137] and 17β-*t*-butyloxy-3-methoxy-9β-estra-1,3,5(10),6,11-hexaene, available from the Heck coupling of (*Z*)-(2-bromoethenyl)bromobenzene and a hexahydro-1*H*-indene derivative. [138]

More work on the CAN oxidation reaction, incorporating other estrone derivatives, such as 17-oxo-14α-methyl-estra-1,3,5(10)-trien-3-yl acetate, is also warranted in order to ascertain the mechanism of this interesting transformation.

Chapter 3

Approaches to the Synthesis of 15,17-Bridged Analogues of Estradiol

A number of ring D modified estradiol analogues have been synthesised since the original discovery that 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol **60** is an orally active estrogen. [31] These include analogues with bridging between C-14 and C-17, [35] between C-14 and C-16, [32] and C-14, C-15 fused ring systems [40] (Figure 3.1).

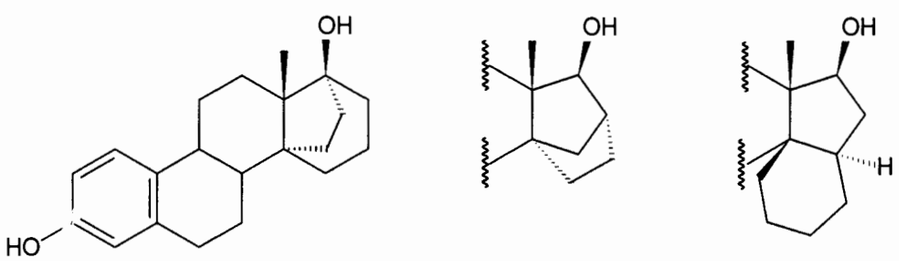


Figure 3.1: Some examples of ring D modified estradiol analogues

As yet, few examples of 15,17-bridged systems have been synthesised, one example is 3-methoxy-15β,17β-ethano-14β-estra-1,3,5(10),8-tetraen-17α-ol, which is one of a number of products resulting from the acid-catalysed rearrangement of 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol (Figure 3.2). [90]

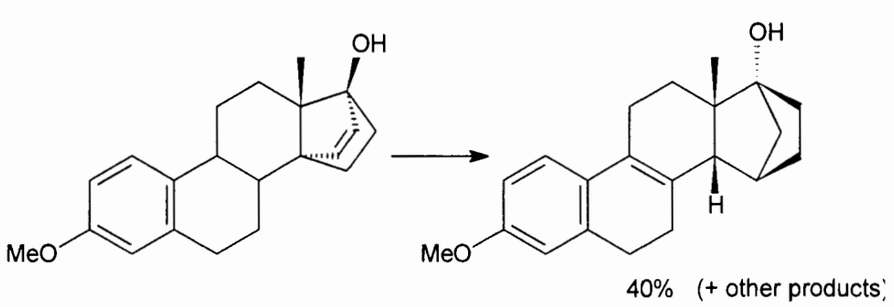


Figure 3.2: Acid-catalysed rearrangement of 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol

As part of the molecular modelling study (Chapter 4), some 15,17-bridged systems were examined and the preliminary evidence indicated that they could well be biologically active. In the light of these predictions, some precursors to 15,17-bridged systems were prepared in order to examine the facility with which a bridge between these two positions can be constructed.

In this investigation, the synthesis of 15α,17α-bridges was studied primarily, as it was recognised that steric hindrance between the 13β-methyl group and the elements of a 15β,17β-bridge could pose a significant impediment to the formation of 15β,17β-bridges.

As an example, a retrosynthetic analysis of 15α,17α-propanoestra-1,3,5(10)-triene-3,17β-diol **A**, identified four synthons (Figure 3.3). Of these, synthons **b** and **c**, requiring the introduction of functionalised 17α- and 15α-alkyl residues, were not considered in this investigation. Further elaboration of synthons **a** and **d** as well as the coupling reactions attempted will be presented in the ensuing section.

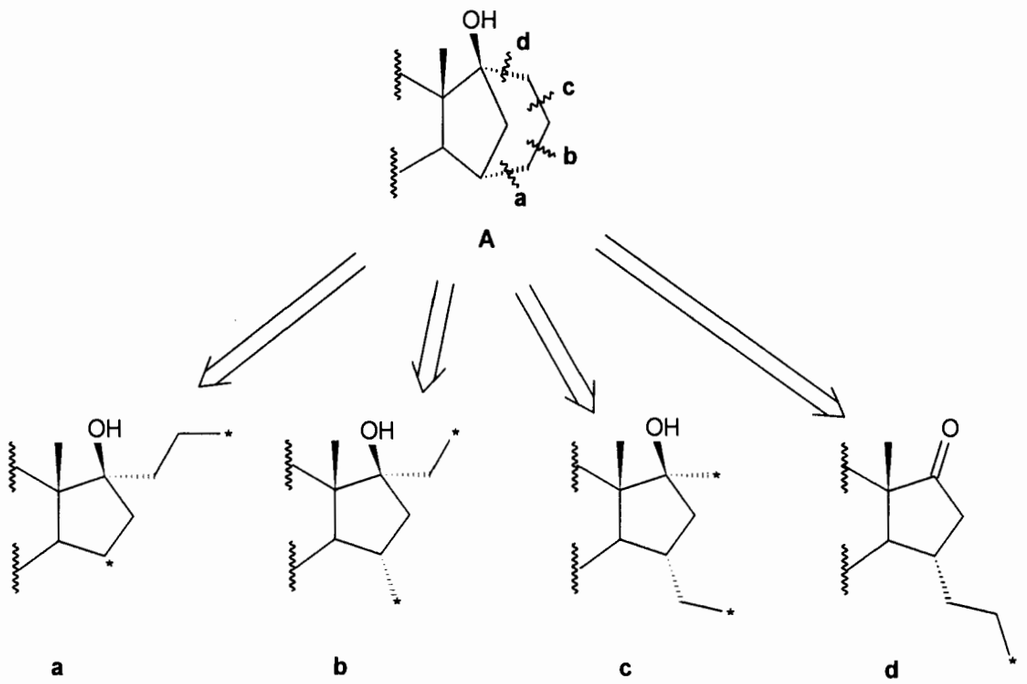
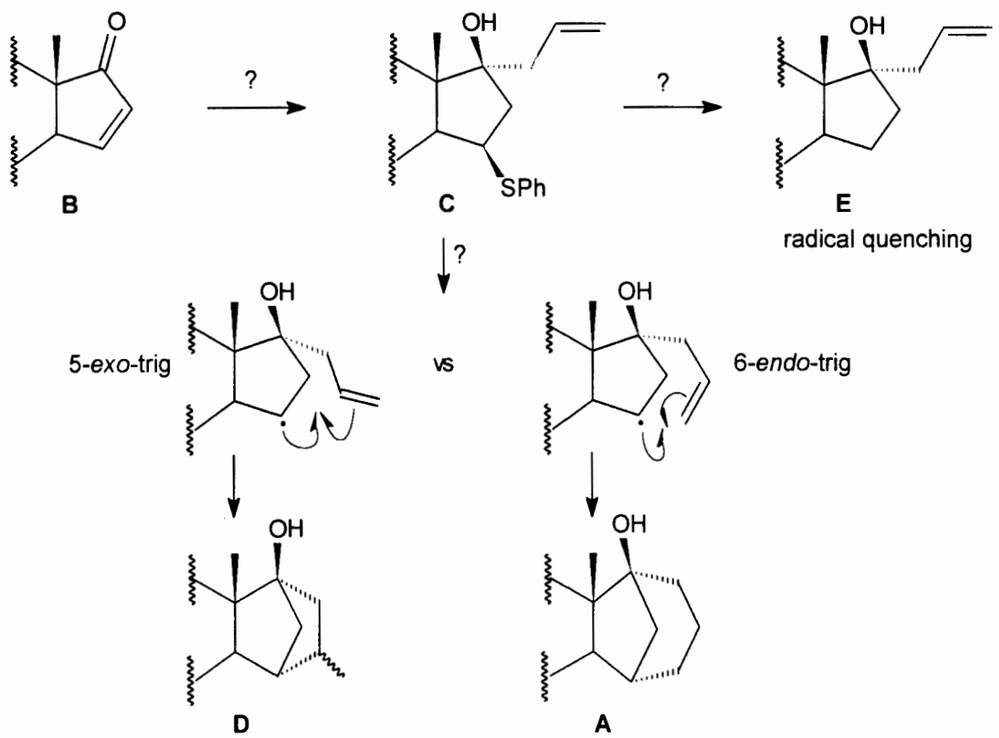


Figure 3.3: Retrosynthetic analysis

3.1 Synthesis and attempted coupling reactions of C-17α and C-15 functionalised derivatives

Synthon **a** requires the introduction of a functionalised 17α-propyl chain, as well as an activating group at C-15. As there is ample precedent for the stereoselective α-face addition of nucleophiles to 17-ketones [139] the introduction of a 17α-propyl moiety was not expected to present any synthetic problems. The introduction of an activating group at C-15 via conjugate addition to the Δ^{15} 17-ketone should also be feasible. [66] Thus, the following synthetic route was envisaged (Scheme 3.1): conjugate addition of thiophenol to the Δ^{15} 17-ketone **B** followed by addition of a 17α-allyl group would provide a precursor for radical cyclisation **C**, to provide either the 15α,17α-ethano compound **D** or the 15α,17α-propano analogue **A** or both.

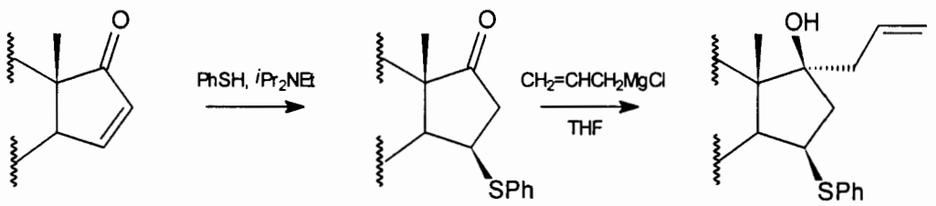


Scheme 3.1: Proposed synthetic route

The well-documented preference for cyclisation reactions of 5-hexenyl radicals to proceed via the 5-*exo* trig pathway [140] should lead to the preferential formation of the 15α,17α-ethano product **D**. The steric constraints imposed upon this reaction pathway might allow the less strained 6-*endo* trig process (leading to **A**) to become an effective

competing reaction, but it is more likely that quenching of the radical prior to cyclisation, to give the 17α-allyl compound **E** will be the major alternative reaction pathway. [140]

The conjugate addition of thiophenol to Δ^{15}-estrone 3-methyl ether **87** has been reported to give the desired 15β-phenylthio 17-ketone **88**. [86] However, no experimental conditions for the reaction, or any characterisation of the product were reported. Accordingly, the Δ^{15} 17-ketone **87** [141] was treated with thiophenol and ethyldiisopropylamine for 3h at 25°C to give a high yield (93%) of a single product, which was readily identified as the desired 15β-phenylthio 17-ketone **88** from spectroscopic and analytical information (Scheme 3.2).



87 **88** **89**

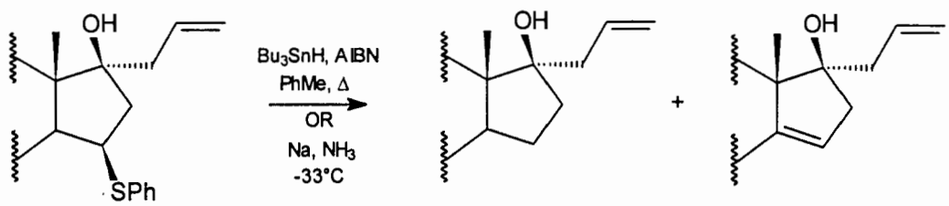
Scheme 3.2

The configuration of the 15β-phenylthio group was assigned from the ^{1}H NMR spectrum, specifically the signals for 14α-H (δ 1.42, dd, *J* 11.2 and 7.0 Hz) and 15α-H (δ 3.49, ddd, *J* 8.0, 7.0 and 1.6 Hz). The small coupling constant between 14α-H and 15α-H indicates the synclinal relationship between the two protons, and hence the configuration at C-15. This information, along with the well established precedent for conjugate addition to Δ^{15} 17-ketones to give rise to 15β-substituted products [66] was considered sufficient proof of the structure.

Allylation of the 15β-phenylthio 17-ketone **88** proceeded smoothly to give the desired 17α-allyl 15β-phenylthio 17β-alcohol **89** (83%). The product was identified from the ^{1}H NMR spectrum, in which signals for both the 15β-phenylthio (δ 7.18-7.40) and the 17α-allyl (δ 5.20, m, 2H; 5.88-6.20, m, 1H) groups were clearly visible. The remainder of the spectroscopic and analytical data fully supported the assigned structure.

Refluxing the 17α-allyl 15β-phenylthio 17β-alcohol **89** with tributylstannane and the radical initiator, AIBN, gave an inseparable mixture of 17α-allyl estradiol **90** and the corresponding Δ^{14}-derivative **91** (*ca* 7:3 by ^{1}H NMR) (52%) as well as some starting

material (20%) (Scheme 3.3). From the ^{1}H NMR spectrum of the product mixture, both the presence of the 17α-allyl group and the absence of the 15β-phenylthio group were observed. The major product, **90**, was identified by comparison with authentic material prepared independently (see next reaction), and the minor product was identified from the doublet of doublets (δ 5.68, *J* 6.0 and 3.2 Hz) for 15-H, characteristic of a Δ^{14}-bond. [142-144] Thus, formation of a 15α,17α-ethano bridge by a 5-*exo*-trig cyclisation appears to be sterically disfavoured, 6-*endo*-trig cyclisation does not occur, and radical quenching is the only reaction pathway observed.



89 **90** **91**

Scheme 3.3

The 17α-allyl-15β-phenylthio 17β-alcohol **89** was also treated with sodium in ammonia [145] in the hope that cyclisation of the intermediate radical would occur. However, simple desulfurisation was expected to be the major reaction pathway. In the event, the only product isolated from this reaction was the 17α-allyl 17β-alcohol **90** in low yield (28%). This product was readily identified by a comparison of its physical properties with literature values [146] and from the ^{1}H NMR spectrum, which clearly showed the loss of the 15β-phenylthio group, and the presence of the 17α-allyl group. This confirmed the identity of the major product of the previous reaction (tributylstannane - AIBN).

It was recognised that extension of the 17α-alkenyl side-chain, might enable the cyclisation process to proceed via a favourable 6-*exo*-trig cyclisation and a less strained transition state, but this was not investigated for the following reason: As the rate of 6-heptenyl cyclisation is significantly slower than that of 5-hexenyl cyclisation [147] radical quenching becomes a significant reaction pathway. [147] Since no cyclisation was observed in the 5-hexenyl system, with radical quenching being the only reaction pathway, it was considered unlikely that a 6-heptenyl cyclisation would proceed in this system. Thus, this approach was discontinued.

The disconnection to synthon **d** (Figure 3.3) appeared to offer the most scope for further retrosynthetic analysis, provided a stereoselective method for introducing a three-carbon fragment at C-15α could be developed. However, achieving the desired cyclisation with C-17 is likely to be demanding due to the distance between the reacting centres. Regioselective functionalisation of the 15α-alkyl moiety would enable intramolecular coupling of the three carbon fragment with the 17-carbonyl group. Thus, the 15α-acetonyl 17-ketone **F**, the 15α-formylethyl 17-ketone **G** and the terminally functionalised (e.g. X = halide) 15α-propyl 17-ketone **H** were identified as real intermediates of synthon **d**. It is evident that all of these share a common precursor, the 15α-allyl 17-ketone **I**. This in turn should be available from the Δ^{15} 17-ketone **B**, by an oxy-Cope rearrangement of the 17α-allyl 17β-alcohol **J**. The overall retrosynthetic plan is depicted in Figure 3.4.

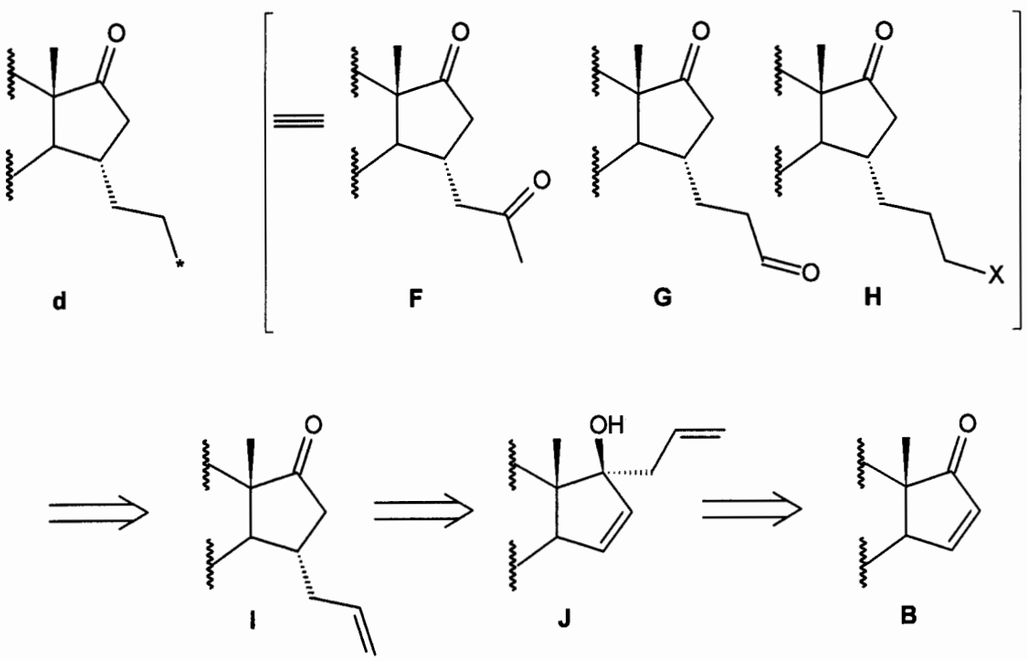
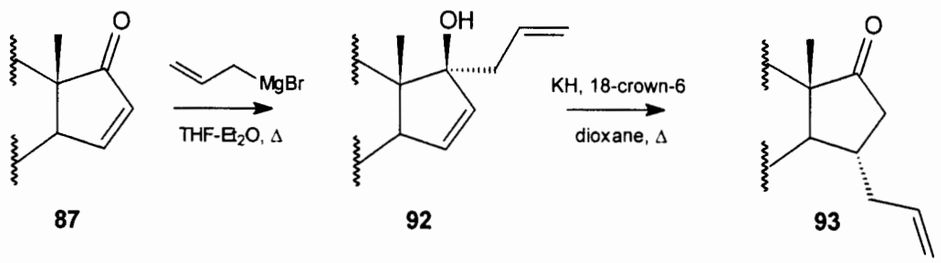


Figure 3.4: Retrosynthesis based upon synthon d

Treatment of the Δ^{15} 17-ketone **87** with allylmagnesium bromide gave the 17α-allyl 17β-alcohol **92** in high yield (97%) (Scheme 3.4). In the ^{1}H NMR spectrum, signals for the

17α-allyl group (δ 5.20, m, 2H; δ 5.82-6.00, m, 1H) and the Δ^{15}-bond (δ 5.67, dd, *J* 6.0 and 3.2 Hz, 15-H; δ 5.99, dd, *J* 6.0 and 1.6 Hz, 16-H) were observed, confirming that the desired addition had indeed occurred.



87 **92** **93**

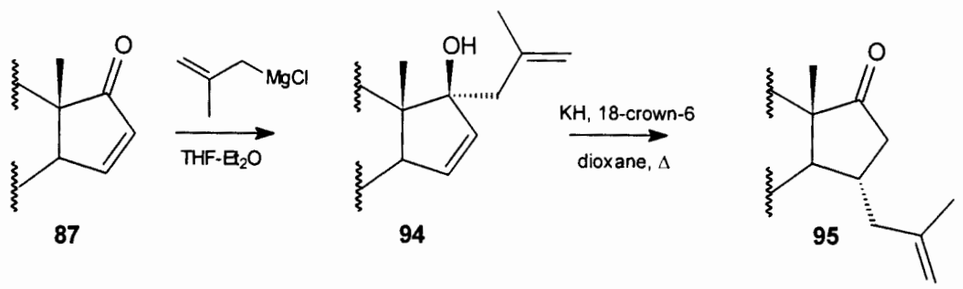
Scheme 3.4

An anion-assisted oxy-Cope rearrangement [148, 149] proceeded sluggishly in THF (incomplete reaction after refluxing for 18h), but on changing the solvent to refluxing 1,4-dioxane, a rapid conversion (1h) resulted in the expected 15α-allyl 17-ketone **93** (94%). An attempted thermal oxy-Cope rearrangement of the 17α-allyl Δ^{15} 17β-alcohol **92** failed to give any conversion, with the starting material isolated unchanged after 18h at reflux in mesitylene.

Compound **93** displayed all the expected spectroscopic and analytical properties, with the diagnostic features being an IR absorption at ν_{max} 1728 cm^{-1} , the signals for 14α-H (δ 1.33, t, *J* 2 x 10.8 Hz) and the 15α-allyl group (δ 4.95, m, 2H; 5.52-5.63, m, 1H). The stereochemistry at C-15 was confirmed by the signal for 14α-H , as only two anti-periplanar coupling partners would give rise to the observed coupling constants.

In order to further explore the scope of this reaction, the corresponding 17α-methallyl 17β-alcohol **94** was prepared (72%) and subjected to similar reaction conditions resulting in a smooth conversion to the 15α-methallyl 17-ketone **95** (75%) (Scheme 3.5). These two compounds, the 17α-methallyl 17β-alcohol **94** and the 15α-methallyl 17-ketone **95**, were readily identified from the expected ^{1}H NMR signals for the methallyl group (δ 1.7-1.8,

3H, s and δ 4.7-5.0, 2 x br. s, 1H each), as well as the remainder of their spectral and analytical data.



Scheme 3.5

Two possible transition states for this oxy-Cope rearrangement are envisaged (Figure 3.5); namely chair-like, **A**, and boat-like, **B**. [148] An examination of these two possibilities indicates that for the 17α-methallyl 17β-alcohol **94** (R = Me), the chair-like transition state is likely to be disfavoured due to steric interaction between the 17^2-methyl group and 14α-H. Thus it appears as if the boat-like transition state would be favoured in this case. As this reaction proceeds efficiently under similar reaction conditions to those used for the 17α-allyl 17β-alcohol **92**, it appears as though the transition state adopted does not significantly affect the reaction outcome.

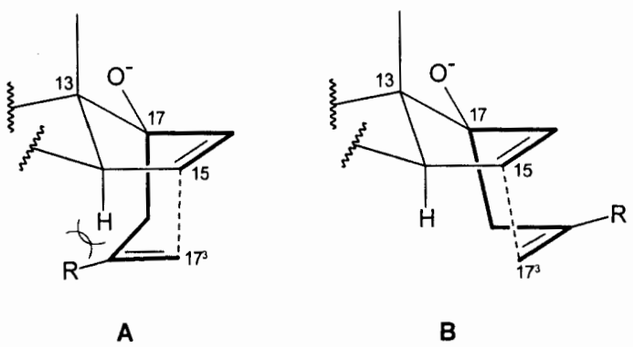
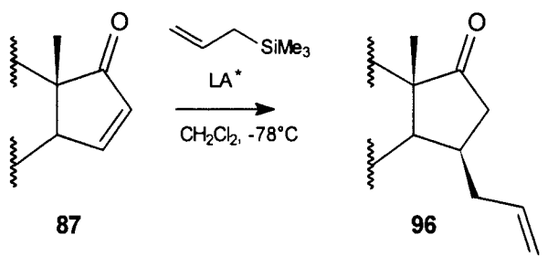


Figure 3.5: The two transition states for the oxy-Cope rearrangement

In addition to the synthesis of the 15α-allyl 17-ketone **93**, the synthesis of the epimeric 15β-allyl 17-ketone **96** was explored in order to examine the feasibility of constructing 15β,17β-bridged compounds.

The first conjugate allylation method to be investigated was the Sakurai reaction. [150] Treatment of the Δ^{15} 17-ketone **87** with titanium tetrachloride and allyltrimethylsilane in dichloromethane at -78°C afforded a low yield (32%) of the desired product (Scheme 3.6). The structure of the 15β-allyl 17-ketone **96** was confirmed by the expected infrared absorption band at ν_{max} 1725 cm^{-1} for the 17-oxo group and ^1H NMR signals at δ 5.04 (2H, m) and 5.65-5.85 (1H, m) for the 15β-allyl group.



87 **96**

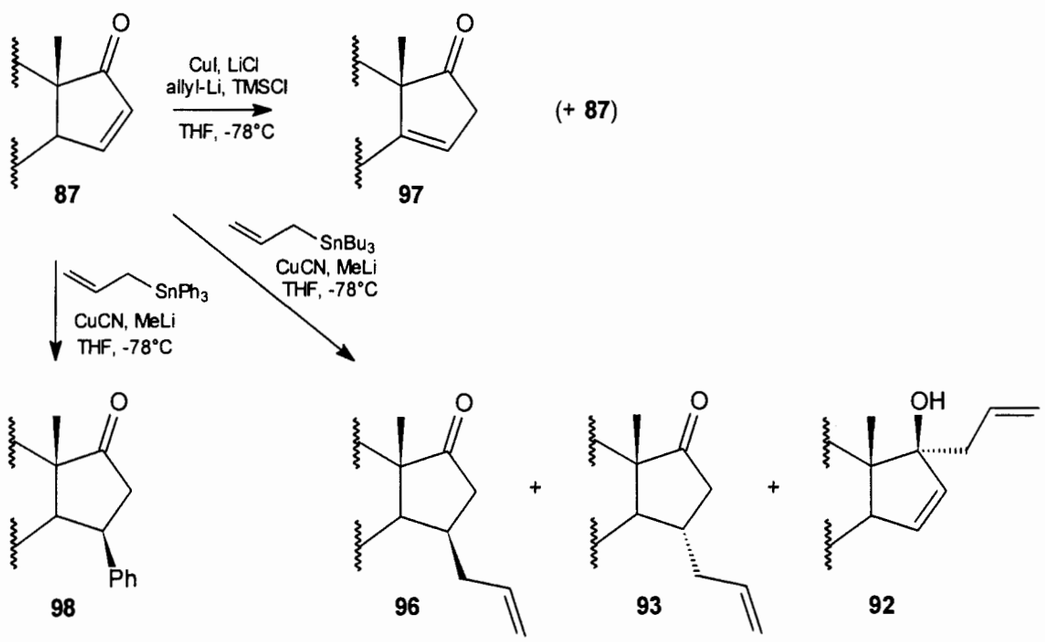
* LA = $TiCl_4$, $SnCl_4$, $EtAlCl_2$

Scheme 3.6

Owing to the low yield obtained for this conversion, a number of different catalysts for this reaction were investigated. Tetra-*n*-butylammonium fluoride, which has been reported to be a superior catalyst for the Sakurai reaction, [151] led to decomposition of the starting material without any conjugate addition product being formed. The use of milder Lewis acids than titanium tetrachloride gave better results, with both ethylaluminium dichloride and tin tetrachloride providing approximately 50% yields of the desired 15β-allyl 17-ketone **96**. However, these improved yields were still unsatisfactory, so alternative methods of introducing the desired 15β-allyl moiety were investigated.

It has been reported that the conjugate allylation of α,β-unsaturated ketones with allylcuprates, in contrast to the conjugate addition reactions of other cuprates, is extremely unreliable. [152, 153] In a recent paper, Lipschutz and co-workers [153] ascribed this to the

instability of allylcopper, but added that the addition of chlorotrimethylsilane to the reaction mixture results in a reproducible conjugate allylation procedure. Treatment of the Δ^{15} 17-ketone **87** with a solution of an allyl copper species (stabilised with chlorotrimethylsilane) in THF at -78°C [153] afforded starting material (26%) and the Δ^{14} 17-ketone **97** (22%); none of the desired product was observed (Scheme 3.7).



Scheme 3.7

Attempts at using the more stable allylcyanocuprate [154] for the introduction of the desired 15β-allyl group were also unsuccessful; however some interesting observations were made regarding the preparation of the reagent. Treatment of the Δ^{15} 17-ketone **87** with allylcyanocuprate, prepared by the addition of allyltributylstannane to the methyl lithium derived cyanocuprate, [153] in THF at -78°C afforded the 1,2-allylation product **92** (67%), which was identified by comparison with authentic material, and an inseparable mixture of 1,4-allylation products **93** (8%) and **96** (25%). From the signal for the angular methyl group [*viz.* 15β-allyl 17-ketone **96**; 13β-Me (δ 1.05) and 15α-allyl 17-ketone **93**; 13β-Me (δ 0.97)] it was possible to estimate the ratio of the two conjugate addition products in this mixture (3:1) (Scheme 3.7). This result is in agreement with literature findings in which

1,2-allylation has been reported to predominate in conjugate addition reactions of allylcyanocuprates to α,β-unsaturated ketones. [153] The loss of β-face selectivity observed for the conjugate addition process appears to be unprecedented. [66, 155] The 15α-allyl 17-ketone **93** might arise from oxy-Cope rearrangement of the 17α-allyl 17β-alcohol **92**, but this has not been investigated.

Interestingly, when allyltriphenylstannane was substituted for allyltributylstannane in the preparation of allylcyanocuprate, a single product, formulated as the 15β-phenyl 17-ketone **98** was isolated (77%). From the analytical data, it was apparent that the addition of a phenyl ligand had occurred, and this was supported by the ^{1}H NMR spectrum. The stereochemistry at C-15 was assigned by literature precedent. [66] Some support for this assignment was obtained from the signal for 15α-H (δ 3.90, m $W_{½}$ 8 Hz), as the signal for 15α-H in other 15β-substituted 17-ketones (for example, 15β-phenylthio 17-ketone **88**) has approximately the same width, and a 15β-H would be expected to have a larger signal width than that observed.

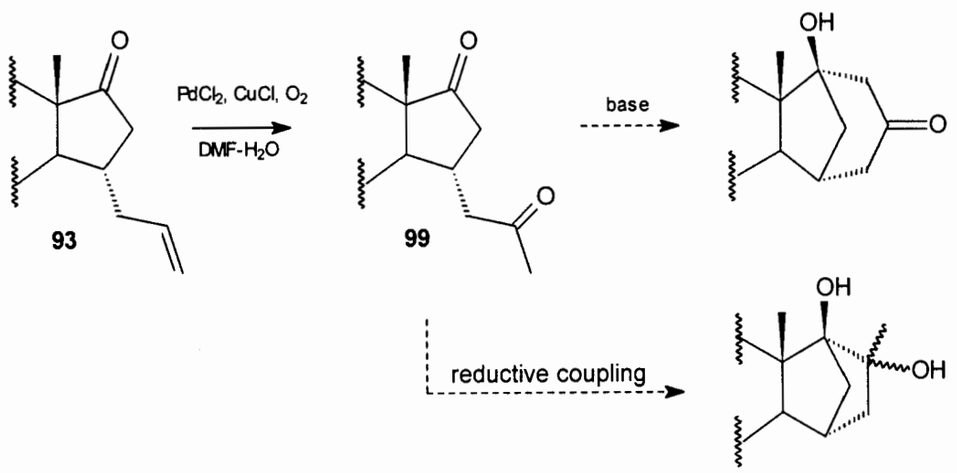
Both allyltributyltin and allyltriphenyltin have been used as a source of allyl ligand in the preparation of allyllithium. [153, 156] However, allyltriphenyltin is clearly not a suitable precursor for the preparation of allylcyanocuprate, possibly due to the phenyl ligand competing with the allyl ligand in the transmetalation reaction, [152] in contrast to butyl ligand transfer. As this result was not useful for the purpose at hand, further investigation was not conducted.

Subsequent and independently to this work, a short communication was published [157] describing the use of the oxy-Cope rearrangement to synthesise the 15α-allyl 17-ketone **93**, and the Lipschutz method [153] for the synthesis of the 15β-allyl 17-ketone **96**. The assignment of stereochemistry in these two products was made in a similar fashion to that discussed in this thesis, and was confirmed by NOE difference spectroscopy.

With the 15α-allyl 17-ketone **93** in hand, a number of different cyclisation pathways to 15α,17α-propano compound were investigated. Wacker oxidation [158] of the 15α-allyl 17-ketone **93** should provide the 15α-acetonyl 17-ketone for an intramolecular aldol

reaction, while hydroboration followed by oxidation should give the 15α-formylethyl 17-ketone for an intramolecular reductive coupling reaction. [159-164] Subsequent modifications of either of these products would provide the target material. As a result of the poor yield for the conversion of the Δ^{15} 17-ketone **87** into the 15β-allyl 17-ketone **96** a similar sequence of reactions on the 15β-allyl 17-ketone **96** was not investigated. However, one cyclisation precursor, the 15β-formylethyl 17-ketone was synthesised by an alternative route, (see p. 108).

Treatment of the 15α-allyl 17-ketone **93** with palladium(II) chloride-copper(I) chloride in a mixture of dimethylformamide (DMF) and water under an oxygen atmosphere (Wacker oxidation) [158] afforded the 15α-acetonyl 17-ketone **99** in high yield (87%) (Scheme 3.8). From the analytical data, it was evident that the addition of oxygen had occurred, and the presence of an acetyl methyl singlet (δ 2.17, 15^3-H_3) in the ^{1}H NMR spectrum provided further proof of the structure.

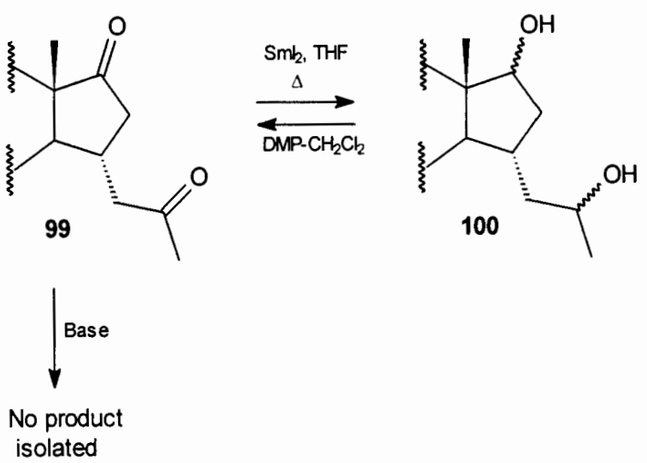


Scheme 3.8

It was hoped that base treatment of the 15α-acteonyl 17-ketone **99** would give rise to a 15α,17α-propano derivative (Scheme 3.8) as the other possible cyclisation reactions all lead to systems containing strained three or four membered rings. However, as the aldol reaction is reversible, it was recognised that the product (if formed) could readily revert back to the starting material. It was also recognised that a reductive coupling of the

15α-acetonyl 17-ketone **99** could provide a 15α,17α-ethano bridged derivative suitable for further modification.

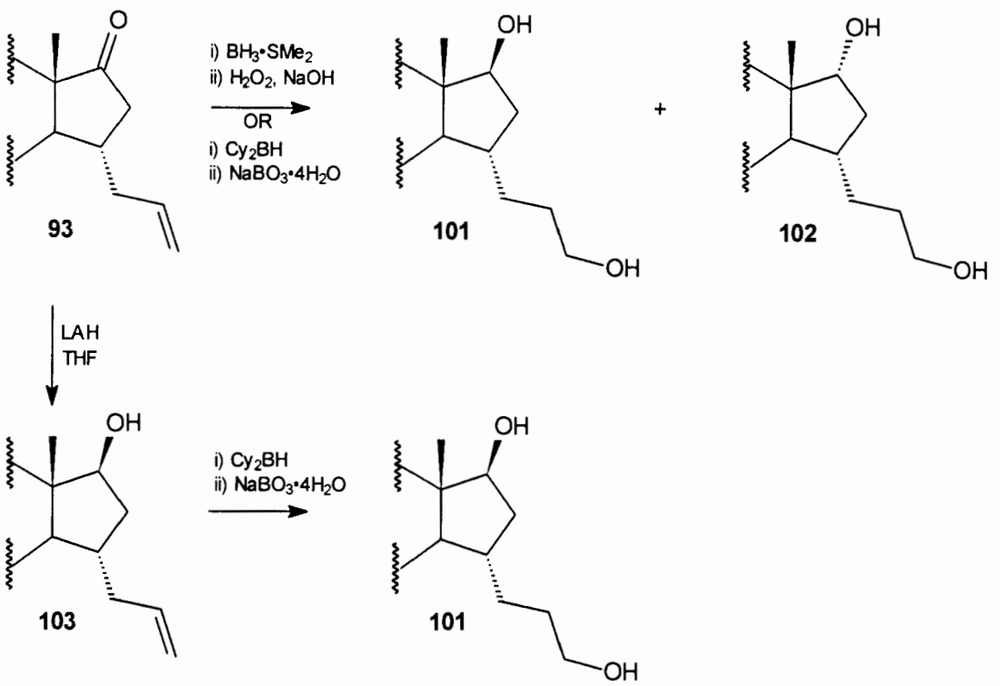
In the event, subjecting the 15α-acetonyl 17-ketone **99** to a range of reaction conditions, including attempts at inducing selective deprotonation at C-17[3] with lithium diisopropylamide or lithium hexamethyldisilazide at -78°C as well as simple equilibration processes (for example, potassium hydroxide in methanol at 25°C) failed to induce any cyclisation (Scheme 3.9). Treatment of the 15α-acetonyl 17-ketone **99** with samarium(II) iodide in refluxing THF [161, 162] failed to induce any coupling reaction, instead a complex mixture of 15[2],17-diols **100** was obtained. Oxidation of this mixture (DMP, CH_2Cl_2) [72] afforded the starting material **99**, thus confirming the structure of the products.



Scheme 3.9

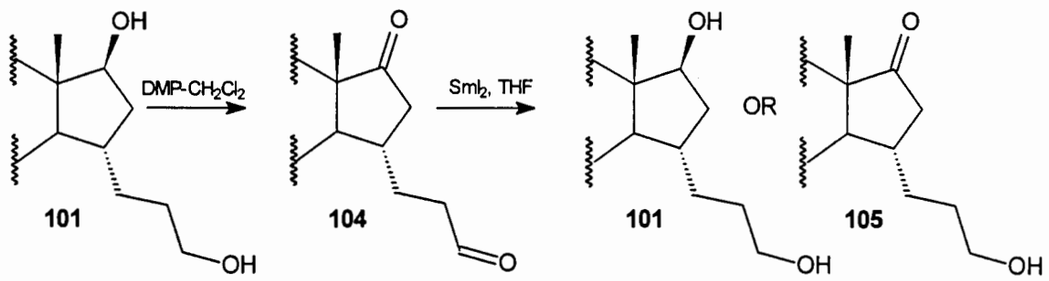
Hydroboration of the 15α-allyl 17-ketone **93** with borane-dimethyl sulfide gave an inseparable mixture of the desired 15α-hydroxypropyl 17ξ-diols **101** and **102** in low yield (39%, *ca.* 1:1 ratio from ^{1}H NMR) (Scheme 3.10). The use of a hindered hydroborating reagent, dicyclohexylborane [165] gave a more satisfactory result, with a single product, formulated as the 15α-hydroxypropyl 17β-alcohol **101** (59%) being obtained. The identity of the product was confirmed by the standard spectroscopic and analytical techniques. The stereochemistry at C-17 was assigned on the basis of dicyclohexylborane hydroboration of

15α-allyl 17β-alcohol **103** (obtained from LAH reduction of the 15α-allyl 17-ketone **93**), which afforded the same product, 15α-hydroxypropyl 17β-alcohol **101** (57%).



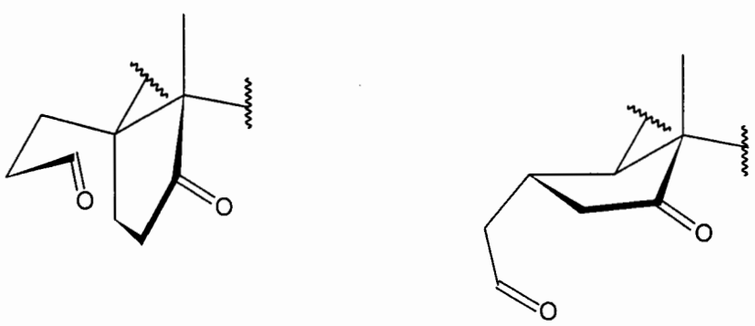
Scheme 3.10

Oxidation of the 15α-hydroxypropyl 17β-alcohol **101** (DMP, CH_2Cl_2) [72] gave 15α-formylethyl 17-ketone **104** (98%), as an unstable oil, thus rendering complete characterisation difficult (Scheme 3.11). However the data set collected supported the assigned structure. Attempted reductive coupling [161, 162] failed to give any 15α,17α-bridged compound. In one reaction, the 15α-hydroxypropyl 17β-alcohol **101** (25%) was the sole isolable product and in a separate experiment a small quantity of the 15α-hydroxypropyl 17-ketone **105** (5%) was isolated.



Scheme 3.11

This result is in contrast with the successful pinacol coupling of 14-(formylethyl)-3-methoxy-14β-estra-1,3,5(10)-trien-17-one **106** [35] and is attributed to the inability of the 15α-side-chain to fold under the α-face of the steroid, due to steric hindrance. From a comparison of the two systems (Figure 3.6), it is clear that in the case of the 14β-formylethyl 17-ketone **106**, the formyl group does not encounter any major steric hindrance in adopting a conformation appropriate for the reaction to occur. In the case of 15α-formylethyl 17-ketone **104**, the formyl ketyl radical is required to fold under ring D, into a sterically crowded environment, so as to react with the ketyl radical generated at C-17. A large energy barrier needs to be overcome in order to adopt this transition state, thus the desired coupling reaction fails and only reduction is observed.

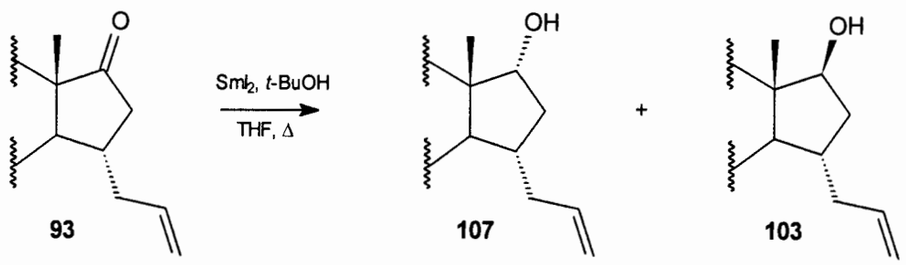


106 **104**

Figure 3.6: A comparison of 14β-formylethyl 17-ketone **106** and 15α-formylethyl 17-ketone **104**

In a final attempt to induce the formation of a 15α,17α-bridge, the 15α-allyl 17-ketone **93** was refluxed with samarium(II) iodide and t-butyl alcohol in THF in the hope that an

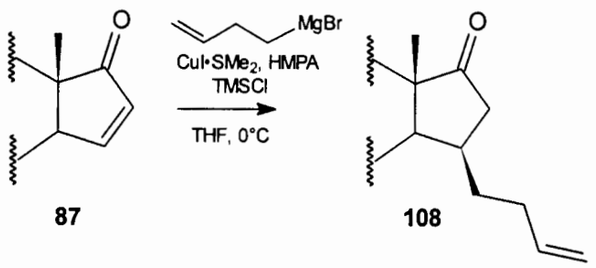
intramolecular ketyl-olefin coupling [166] would result. After 40h, a mixture of the 15α-allyl 17α-alcohol **107** (26%) and the 17β-epimer **103** (47%) was obtained, along with some starting material (15%) (Scheme 3.12). The major product was identified through a comparison with authentic material prepared previously (Scheme 3.10), and the minor product was identified from the ^{1}H NMR spectrum which clearly showed the presence of the 15α-allyl group (δ 5.02, m, 2H; 5.8, m, 1H) and 17β-H (δ 3.70, d, *J* 5.3 Hz).



Scheme 3.12

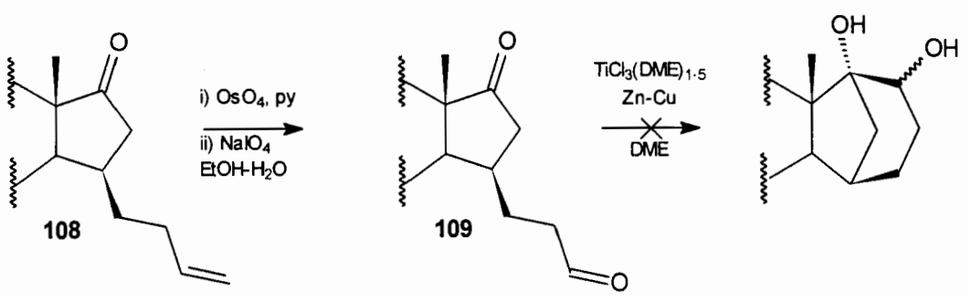
In conjunction with this study some attempts at constructing 15β,17β-bridged analogues were also investigated. The first of these was the reductive coupling of the 15β-formylethyl 17-ketone **109**. The poor yield obtained for the synthesis of the 15β-allyl 17-ketone **96** from the Δ^{15} 17-ketone **87** resulted in an alternative approach (in comparison with the 15α-series) towards the 15β-formylethyl 17-ketone **109** being investigated.

Conjugate butenylation of the Δ^{15} 17-ketone **87** was accomplished with a modified copper catalysed Grignard reaction to give the 15β-butenyl 17-ketone **108** (80%) (Scheme 3.13). The structure of **108** was confirmed by the expected infrared absorption band at ν_{max} 1725 cm^{-1} for the 17-oxo group, and ^{1}H NMR signals for the 15β-butenyl group (δ 4.95-5.10, 2H, m; δ 5.70-5.92, 1H, m).



Scheme 3.13

Treatment of the 15β-butenyl 17-ketone **108** with osmium tetroxide followed by oxidative cleavage of the resultant mixture of diols gave the desired 15β-formylethyl 17-ketone **109** (72% overall yield) (Scheme 3.14). The structure of this product was evident from the infrared absorption at ν_{max} 1725 cm^{-1} for the two carbonyl groups and the low-field singlet for 15^3-H (δ 9.8). Treatment of the 15β-formylethyl 17-ketone **109** with a titanium(III) chloride-dimethoxyethane complex [nominally $TiCl_3(DME)_{1.5}$] [159] and a zinc-copper couple in dimethoxyethane (McMurray coupling) [159, 160] initially at 0°C (for 30 min), and subsequently at 25°C for 18h failed to induce any reaction (TLC). On refluxing for 4h, a complex mixture, from which no steroidal products could be isolated, was formed. This negative result, coupled with the failure to induce any cyclisation in the 15α-formylethyl 17-ketone **104** led to this approach being discontinued.

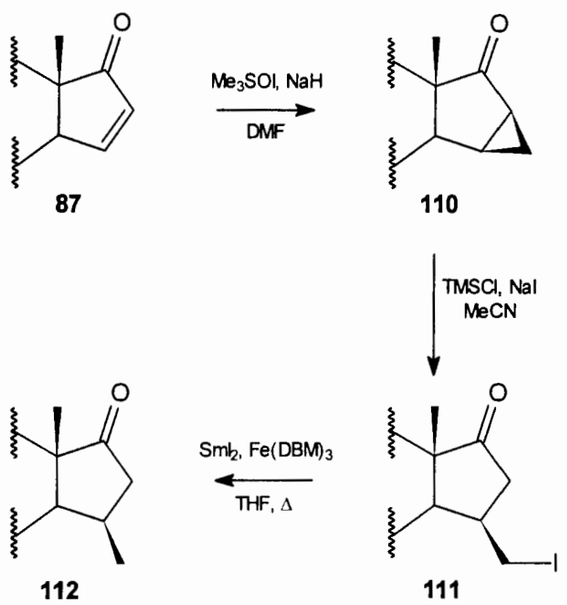


Scheme 3.14

The final method for the synthesis of a 15β,17β-bridge to be examined was the recently reported samarium(II) iodide induced Barbier-type intramolecular coupling of iodoalkyl side-chains with cyclic ketones to form bicyclo[m.n.1]alkan-1-ols. [167] In particular, the

reported cyclisation of 3-(iodomethyl)cyclopentan-1-one to give bicyclo[2.1.1]hexan-1-ol [167] led to the synthesis and coupling of the corresponding 15β-iodomethyl 17-ketone **111** being investigated.

Following a literature procedure, [168] conjugate methylenation of the Δ^{15} 17-ketone **87** with a mixture of trimethylsulfoxonium iodide and sodium hydride in DMF [169] gave 15β,16β-methylene-3-methoxyestra-1,3,5(10)-trien-17-one **110** [168] in quantitative yield (Scheme 3.15).



Scheme 3.15

Treatment of the 15β,16β-cyclopropyl 17-ketone **110** with chlorotrimethylsilane and sodium iodide in acetonitrile [170] afforded the desired 15β-iodomethyl 17-ketone **111** in reasonable yield (60%). From the analytical data, it was clear that addition of iodine had occurred, and the spectroscopic data confirmed this. The assignments of 15^1-$H_{pro\text{-}R}$ (δ 3.24, dd, *J* 12.8 and 2.9 Hz) and 15^1-$H_{pro\text{-}S}$ (δ 3.50, dd, *J* 12.8 and 9.7 Hz) in the ^{1}H NMR spectrum were made on the assumption that the C15-$C15^1$ bond was locked as a single rotamer, due to steric hindrance between the 13β-Me and the 15β-iodomethyl groups. This would lead to the two protons on $C\text{-}15^1$ being non-equivalent, readily accounting for the observed coupling constants (Figure 3.7).

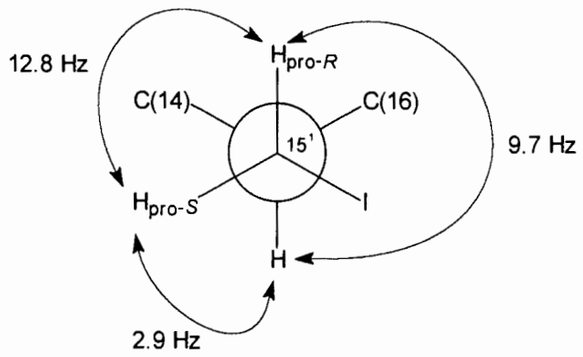


Figure 3.7: Newman projection along the 15^1,15-bond of the 15β-iodomethyl 17-ketone **111**, with the observed coupling constants indicated

On refluxing the 15β-iodomethyl 17-ketone **111** with samarium(II) iodide and catalytic tris-(dibenzoylmethido)iron(III) [167] $[Fe(DBM)_3]$ in THF a slow reaction, yielding 15β-methyl 17-ketone **112** (38%) as the sole product, resulted. From both the ^1H NMR and infrared spectra, it was evident that no cyclisation had occurred, and the product was identified by comparison with authentic material. [171] Thus, it appears as though the additional steric constraints imposed by the steroid prevents this cyclisation from occurring unlike the simple 3-(iodomethyl)-cyclopentan-1-one. [167] As this is probably the most strained example of a 15,17-bridged analogue that can be envisaged, the failure to achieve this cyclisation, while disappointing, does not mean that this approach will not succeed. Once a method for synthesising other chain-extended 15-iodoalkyl derivatives has been developed the applicability of this methodology can be re-evaluated.

3.2 Conclusions

Although the primary objectives of this study, namely the synthesis of 15,17-bridged estradiol analogues have not been accomplished, several aspects of the reactivity of the precursors has been documented. In addition, from this brief investigation, it is has been demonstrated that the formation of 15,17-bridged estradiol analogues by coupling a 15-functionalised alkyl chain with C-17 does not appear to be feasible.

The failure of the 17α-allyl group to couple with a radical at C-15 was somewhat surprising in the light of the successful oxy-Cope rearrangement, which clearly indicates that a 17α-allyl functionality is capable of 'reaching' to C-15. Possible extension of this side-chain might enable this reaction to proceed successfully.

Future work in this area should rather concentrate on attempting to couple functionalised alkyl fragments attached to C-15 and C-17 (Scheme 3.3; synthons **b** and **c**) as this should facilitate a more ready cyclisation.

Chapter 4

Molecular Modelling Study of Ring D Modified Estradiol Analogues

Two broad objectives were envisaged for this work: firstly to find an explanation for the biological activities observed in ring D bridged estradiol analogues and then to develop a basis for predicting the activity of potential synthetic targets.

A number of theoretical methods exist for determining the conformations of molecules. A firmly established method is that of molecular mechanics. A basic outline of this procedure and some of the limitations thereof will be presented.

From a molecular mechanics perspective, molecules are considered to be a collection of masses that interact with one another via (almost) harmonic forces. Potential energy functions [174] are used to describe the interactions between the nuclei. These interactions; namely bond stretching, (E_s), angle bending (E_b), van der Waals interactions (E_{vdw}), torsional interactions (E_{tor}) and electrostatic interactions (E_{elec}), all contribute to the total energy (E_{total}) of the molecule, leading to an equation describing the system [1].

$$E_{total} = E_s + E_b + E_{vdw} + E_{tor} + E_{elec} \quad [1]$$

A more refined molecular mechanics model will take cross term interactions, such as stretch-bend, into account as well, but these terms are usually small and are often neglected. [173]

Any deviations from the 'ideal' molecular geometry will result in an increase in energy. [173] Through a process of energy minimisation using these potential energy functions, a minimum energy conformation of the molecule can be obtained. A number of different methods for performing this process of energy minimisation exist, [174] but will not be discussed here.

The major problem associated with the energy minimisation process is that the minimum energy conformation obtained is largely dependent on the initial geometry of the molecule. Most minimisation algorithms can only go in a 'downhill' direction and are unable to surmount energy barriers in order to locate a lower energy conformation elsewhere on the potential energy surface. [175] For example, if a cyclohexane molecule was placed in a boat-like conformation and minimised, the structure would minimise to the boat conformation and the process would stop. The chair conformation, which has a lower energy would not be found by this procedure.

A large number of methods have been developed to search the conformational space of a molecule, in order to determine the minimum energy conformations. These range from systematically rotating every single bond in the molecule and determining the energy of each possibility, to randomly changing the 'current' structure to give a new structure which is then minimised, repeating this latter process a large number of times. The systematic method rapidly becomes impossible to implement as the number of rotatable bonds increases. The random method suffers from a lack of certainty that the entire conformational space has been covered and that all energy minima, including the global minimum, have been located. [175]

A further limitation of molecular mechanics, and molecular modelling in general, is that the effects of solvent are often not included as this renders the calculation extremely time intensive. The energy minima determined are, in effect, in vacuum, and may have limited applicability to the solution state, where most biological processes occur. Attempts have been made to incorporate solvent effects in the calculation [175] but these are still imperfect. [175] For the purposes of this thesis, solvent effects were excluded, as it was considered unlikely that they would have a substantial effect on the conformations obtained.

What makes the molecular mechanics method so attractive though, is that through careful parameterisation of the force-field (the potential energy functions used to describe the system) these calculations are capable of reproducing experimentally determined geometries within experimental error, without being too computationally intensive. [173] For

these reasons, the molecular mechanics method was chosen over the more sophisticated *ab initio* and semi-empirical methods.

The first stage of this computational study was to establish the structure of the compound under investigation. It is known that the conformation observed in the solid state of most uncharged organic molecules, such as steroids, is at or near a local energy minimum. [23] Additionally, if the global minimum structure is significantly lower in energy than other local minimum energy conformations it is highly probable that a crystal incorporating this conformation will be formed preferentially. [23] Thus a combination of X-ray crystallography and molecular mechanics was envisaged as being suitable for establishing the structure of the molecule under investigation.

Since steroids, and especially estra-1,3,5(10)-trienes are fairly rigid molecules the number of possible conformations is limited, and in most cases the minimum energy structure is likely to have the ring B half chair, ring C chair conformation. [176] Most of the conformational flexibility of these molecules is located in the B ring region, where the 7α,8β-half chair conformation is generally favoured, but structures with the alternative 8β-envelope conformation have also been observed. [176] Ring D is another source of flexibility, as a result of pseudorotation, [176] however, for most of the molecules studied in this thesis, there is a conformational restraint placed upon ring D, removing this flexibility.

For all the molecules studied in this thesis, the simple procedure of manually distorting each of ring B and C into the respective boat, chair and/or half-chair conformations followed by energy minimisation was employed. Apart from the skeletally modified analogues, which will be discussed in a separate section, the lowest energy structure was invariably the ring B half-chair ($^{8}H_{7}$), ring C chair ($^{8}C_{12}$) conformation. In many cases it proved impossible to minimise the molecule in any other conformation. No flexibility in ring D was observed, even in cases where this might be expected. This could be due to inaccurate parameterisation of the force-field. All comparisons, unless otherwise stated, were performed on the minimum energy conformer.

Once the minimum energy structure (or structures if they are close in energy) has been determined, the next stage is to somehow compare them with the natural hormone template, estradiol. A comparison of this type allows the features which lead to enhanced binding affinity, as well as those which lead to decreased affinity to be identified. It is assumed that estradiol binds to the receptor in a conformation approximating that of the global minimum energy structure, [6, 22, 173, 177] hence it is reasonable to assume that the test molecule will adopt a conformation that allows for the best possible overlap with estradiol.

A number of different protocols for this type of comparison can be envisaged, ranging from a purely manual superimposition of the molecules to the computationally intensive methods which have been developed precisely for this purpose, for example comparative molecular field analysis (CoMFA). [6-13, 177] As this project was merely an initial foray into this area, these latter methods were not investigated.

The comparison was performed by superimposing the two oxygen and ring A atoms of the test material with the corresponding atoms of estradiol using a simple root-mean-square fitting procedure (Figure 4.1). It was reasoned that by superimposing the minimised conformations of both the test material and estradiol, systematic inaccuracies in the molecular geometry would cancel one another out, thus enabling a reasonable comparison to be conducted.

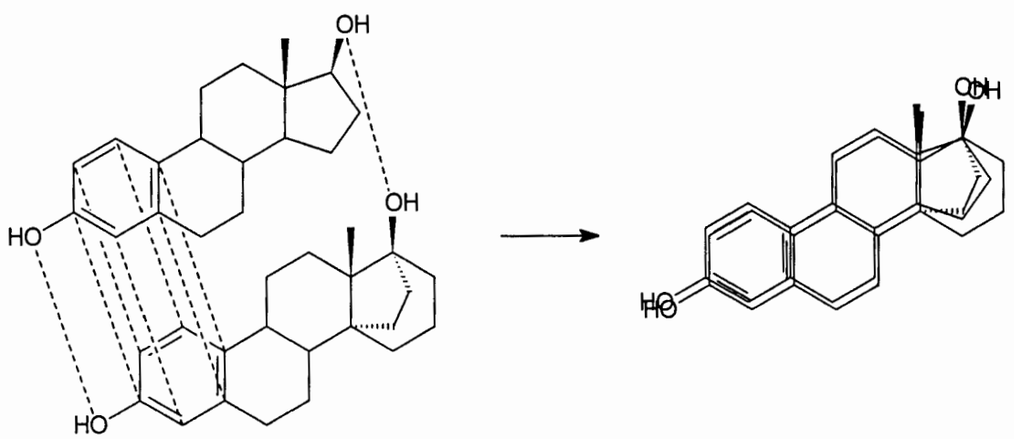


Figure 4.1: A schematic depiction of the superimposition process indicating the paired atoms

These selections of atom pairs for the superimposition were based upon the postulated method of estradiol binding to the receptor. The phenolic A ring initially binds strongly to the receptor through the 3-hydroxy group, followed by the 17β-hydroxy group interacting with another part of the receptor to induce the desired biological response. As both functional groups are essential for biological activity, it was decided to include both in the superimposition. This choice could introduce some bias into the derived model, a criticism which could equally well be applied to any other selection of atoms. Alternative models which were considered but not investigated were that of superimposing only the atoms of ring A and superimposing all the atoms of rings A, B and C, C-17 and O-17.

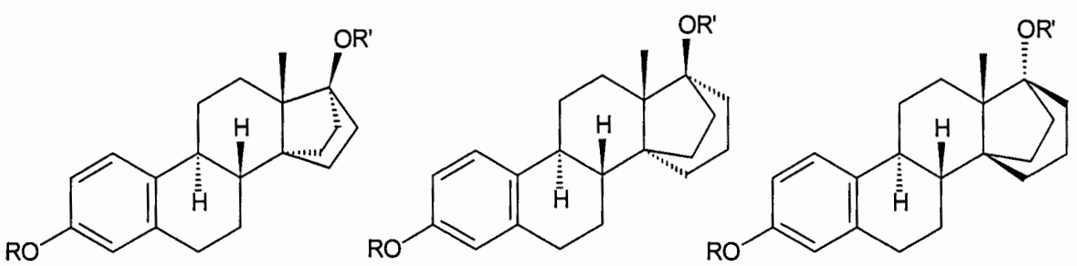
In addition to the superimposition studies, several molecular dynamics simulations were performed in order to assess the conformational flexibility of these ring D modified estradiol analogues. The molecular dynamics process aims to reproduce the time-dependent motional behaviour of a molecule. [175] The molecule is provided with energy (determined by the temperature at which the simulation is run) and the atoms are allowed to move freely, restrained only by the force-field. In this way, it is possible to analyse the dynamic behaviour of a molecule at the desired temperature. [175]

In most cases, the molecule under investigation was observed to adopt just one other conformation and this for a brief period only. In these instances, the initial ground state is obviously far more stable, and thus is the only conformation used for the superimposition studies.

4.1 Comparison of calculated and experimental structures

In order to assess the validity of the calculated minimum energy structures that will be used in the superimposition studies, crystal structures of three ring D bridged estradiol analogues were determined and compared to the calculated minimum energy conformations (Figure 4.2). Two of these determinations were conducted as a part of this thesis (see p. 214 for details), the third was conducted in a separate investigation. [37]

The three compounds investigated were 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol **60**, 14,17α-propanoestra-1,3,5(10)-triene-3,17β-diol **114** and 14,17β-propano-14β-estra-1,3,5(10)-triene-3,17α-diol **116**, (Figure 4.2) as they form the 'core' set of ring D modified estradiol analogues upon which much of this work has been based.



60 R = R' = H
113 R = Me, R' = Ac
114 R = R' = H
115 R = Me, R' = Ac
116 R = R' = H
117 R = Me, R' = H

Figure 4.2: Structures used for X-ray crystallographic determinations

The crystal structure determinations were by necessity carried out on protected forms of the analogues (Figure 4.2, **113**, **115** and **117**), as no crystals suitable for X-ray diffraction could be obtained for the diols **60**, **114** and **116** (Figure 4.2). This was not anticipated to have a significant effect on the observed conformations. [176] However, the presence of the protecting groups will affect intermolecular contacts in the unit cell and this in turn could influence the observed conformations.

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate, **113** [57] was found to possess two crystallographically independent molecules in the unit cell, both of which exhibit a conformation similar to the calculated minimum energy form of **60**, with some deviation observed in ring B. This similarity is evident from a comparison of the puckering parameters [178, 179] (also see Appendix 2) for these two rings (Table 4.1).

Table 4.1: Puckering parameters for the experimental and calculated structures of the 14α,17α-ethano derivatives **60** and **113**

Structure	Ring B Conf.	Q/Å	θ/°	ϕ/°	Ring C Conf.	Q/Å	θ/°	ϕ/°
113 (X-ray)	^8E, $^8H_7$	0.524	127.3	10.8	$^8C_{12}$	0.546	4.6	232.1
113 (X-ray)	$^8H_7$	0.521	129.4	18.7	$^8C_{12}$	0.521	4.0	233.3
60 (calc.)	$^8H_7$	0.488	134.5	26.4	$^8C_{12}$	0.547	4.8	283.1

3-Methoxy-14,17α-propanoestra-1,3,5(10)-trien-17β-yl acetate **115** also had two crystallographically independent molecules in the unit cell. As was observed for the 14,17α-ethano bridged compound **113**, both of the crystallographically independent molecules displayed a conformation similar to the calculated minimum energy conformation, with some deviation in ring B. Table 4.2 shows the puckering parameters for rings B and C. In both the calculated and the experimentally determined structures, the 14α,17α-bridging ring was in a slightly distorted chair conformation.

Table 4.2: Puckering parameters for the experimental and calculated structures of the 14α,17α-propano derivatives **114** and **115**

Structure	Ring B Conf.	Q/Å	θ/°	ϕ/°	Ring C Conf.	Q/Å	θ/°	ϕ/°
115 (X-ray)	$^8H_7$	0.518	130.0	19.3	$^8C_{12}$	0.528	6.4	285.2
115 (X-ray)	$^8H_7$	0.544	128.0	16.8	$^8C_{12}$	0.502	11.2	274.2
114 (calc.)	$^8H_7$	0.492	134.2	25.9	$^8C_{12}$	0.568	13.5	278.7

In the case of 3-methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17α-ol **117**, [37] four crystallographically independent molecules were present in the asymmetric unit, each possessing a different conformation. The main source of this deviation was in ring B which was found to adopt a different conformation in each structure. The calculated minimum energy structure of **116** has ring B in the expected half-chair ($^8H_7$) conformation, while the experimentally determined structures have ring B in a variety of conformations (envelope, boat, twist-boat and screw-boat). This is summarised in Table 4.3.

Table 4.3: Puckering parameters for the experimental and calculated structures of the 14β,17β-propano derivatives **116** and **117**

Structure	Ring B Conf.	Q/Å	θ/°	ϕ/°	Ring C Conf.	Q/Å	θ/°	ϕ/°
117 (X-ray)	$^{5}T_{9}$	0.597	104.3	317.4	$^{8}C_{12}$	0.539	6.9	192.7
117 (X-ray)	$^{5}T_{9}$	0.535	109.5	321.9	$^{8}C_{12}$	0.540	4.2	151.8
117 (X-ray)	^{8}E	0.510	129.9	353.0	$^{8}C_{12}$	0.542	8.4	176.9
117 (X-ray)	$^{8}S_{9}$	0.534	115.5	330.3	$^{8}C_{12}$	0.539	6.3	171.7
116 (calc.)	$^{8}H_{7}$	0.495	133.1	31.0	$^{8}C_{12}$	0.539	4.7	88.5

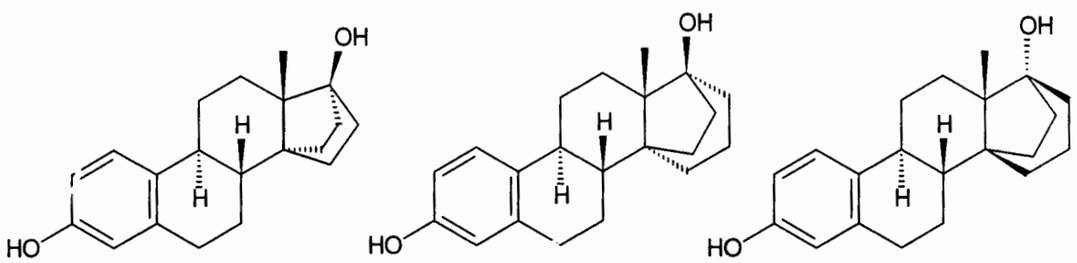
Upon energy minimisation, two of these conformations adopted the calculated minimum energy structure, while the other two converged upon a slightly higher energy structure with ring B in a boat-lie conformation. This discrepancy between the calculated and observed structures is unlikely to be due to the presence of the protecting group, as this has not significantly affected the previous determinations.

The space group of **117**, P1, has a natural number of one. In **117**, however, the number of molecules in the asymmetric unit is four. In addition to this unusual observation, there exists a hydrogen bonding network between the four molecules and a water molecule. The presence of hydrogen bonds is obviously not accounted for in the calculation, and may be responsible for the molecules adopting higher energy conformations in the crystal lattice.

Although this is a small comparison set, if all three crystal structure determinations are taken into consideration, the molecular conformations obtained by calculation appear to be reasonable structures for subsequent superimposition studies. However, the force-field does not accurately reproduce the observed ring B geometry, and appears to be insensitive to possible conformational transmission effects. The use of these structures for the superimposition studies is further justified by the fact that they possess the most 'estradiol-like' conformation. The lowest energy conformations of all the natural backbone estradiol analogues were then confidently used for superimposition purposes. Each of these will be discussed in turn. An explanation for the observed biological activities based solely upon the experimentally observed structures is presented in Section 4.4.

4.2 Analysis of ring D modified estradiol analogues

The first three structures to be considered in this study were the 'core' molecules, the 14α,17α-ethano **60**, [57] 14α,17α-propano **114** [34] and 14β,17β-propano **116** [35, 37] analogues of estradiol. These structures are indicated in Figure 4.3, along with their observed binding affinity, expressed as a competition factor (CF). [24] This measurement is explained in more detail in Appendix 1, but to summarise, the smaller the CF, the higher the activity. Any molecule with a CF of less than one is a more effective at binding to the estradiol receptor than estradiol itself.



60 (CF 0.6) **114** (CF 1.5) **116** (CF 69)

Figure 4.3: 14,17-Bridged estradiol analogues **60**, **114** and **116**

In order to assess the relative flexibility of ring D modified estradiol analogues, the 14,17α-ethano compound **60** was subjected to a molecular dynamics simulation. It was assumed that other ring D modified estradiol analogues in the natural series would display similar conformational flexibility. It is recognised that this is a major assumption to make, as the conformational transmission effects of the different bridging ring sizes on the conformations of both ring B and ring C will differ. [180-182] However, as a first approximation it was considered reasonable.

During the simulation, two torsion angles which provide an indication of the conformations of ring B and ring C were measured, $\phi_{6,7,8,9}$ (ϕ_1) and $\phi_{8,9,11,12}$ (ϕ_2). In the ground state conformation, ϕ_1 = -60.2° and ϕ_2 = 48.6°. If ring B were to invert into the boat conformation, ϕ_1 would change to approximately 0° and if ring C were to adopt the boat conformation, ϕ_2 would also change to approximately 0°.

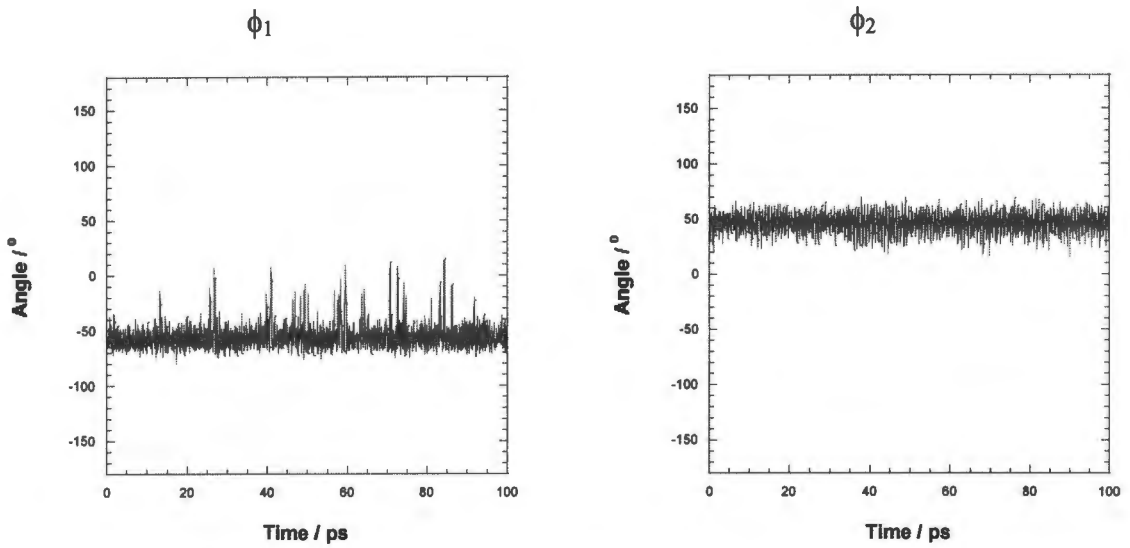


Figure 4.4: Results of the molecular dynamics simulation of 14α,17α-ethano derivative **60**. ϕ_1 ($\phi_{6,7,8,9}$) Indicates the relative flexibility of ring B, and ϕ_2 ($\phi_{8,9,11,12}$) that of ring C.

From the results of this simulation (Figure 4.4), it is evident that some inversion of ring B occurs. The resulting conformation appears to be an unfavourable, high energy structure as it rapidly reverts to the more stable conformer (resembling the ground state conformation). Ring C does not undergo any inversion and remains in the chair conformation. Hence, as expected, the only source of flexibility is in ring B, and inversion of this ring results in a less favourable conformation.

The additional steric bulk introduced by the ring D bridge is clearly displayed by superimposing **60** with estradiol. Apart for the ring D environment, there is a remarkably close correspondence between the two molecules (Figure 4.5).

Figure 4.5: Superimposition of 14α,17α-ethano analogue **60** with estradiol

The major differences are obviously the 14α,17α-ethano bridge, and the conformation of ring D, which is forced to adopt a ^{13}E conformation by the bridge. The introduction of a

hydrophobic substituent to the 17α-position is known to either enhance receptor binding (17α-ethynyl) or moderately decrease it (17α-methyl), [26] thus the 14α,17α-ethano bridge appears to have an effect similar to that of the 17α-ethynyl substituent, enhancing binding. The slightly modified ring D conformation does not appear to inhibit binding in any way.

Increasing the size of the 14α,17α-bridge, to give the 14α,17α-propano analogue **114**, appears to have very little effect on receptor binding. As can be seen from the superimposition of the 14α,17α-propano compound **114** with estradiol (Figure 4.6), the molecules are remarkably similar.

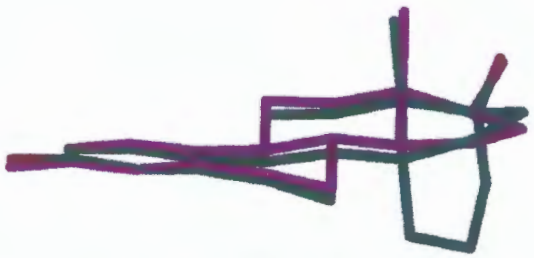


Figure 4.6: Superimposition of 14α,17α-propano derivative **114** with estradiol

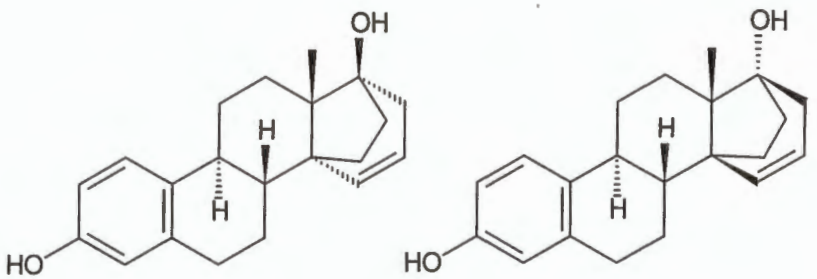
As is the case for the 14α,17α-ethano compound **60** the major difference is the additional steric bulk introduced on the α-face of ring D, which appears to be readily accommodated by the receptor. However, the slight increase in steric bulk does appear to reduce the binding affinity, indicating that the receptor pocket is relatively small. Very little ring D deviation is observed. This molecule (**114**) possesses a more 'estradiol-like' conformation than the 14α,17α-ethano compound **60**, but this is not expected to influence the activity.

In contrast, increasing the size of the 14β,17β-bridge to give the 14β,17β-propano derivative **116** results in major inhibition of binding affinity. The superimposition with estradiol (Figure 4.7) reveals some possible explanations for this loss of activity.

Figure 4.7: Superimposition of the 14β,17β-propano analogue **116** with estradiol

It can be seen that the overall superimposition with estradiol is poorer in this case than in the previous two. The observed loss of binding affinity might be ascribed to two factors; either steric interactions between the receptor and the 14β,17β-propano bridge (specifically C-17[1] and C-17[2]) destabilises the receptor-ligand interaction or the 17α-hydroxy group is protruding into a hydrophobic region of the receptor.

The observed difference in binding affinity between the 14α,17α-propano compound **114** and the 14β,17β-propano compound **116** is increased upon the introduction of unsaturation into the bridging ring. Thus, the 14α,17α-propeno compound **118** [34] (Figure 4.8) has an extremely high receptor affinity while the corresponding 14β,17β-propeno compound **119** [37] (Figure 4.8) is completely inactive.



118 (CF 0.4) **119** (CF 470)

Figure 4.8: Ring D bridged estradiol analogues **118** and **119**

Similarly to the previously described 14α,17α-bridged compounds (**60** and **114**), the 14α,17α-propeno compound **118** displays a close correspondence to estradiol with respect to the conformation of rings B, C and D (Figure 4.9). The additional steric bulk on the α-face appears to be readily accommodated by the receptor, as is the case for **60** and **114**.

The introduction of unsaturation flattens the bridging ring, and this appears to enhance the binding affinity.

Figure 4.9: Superimposition of 14α,17α-propeno compound **118** with estradiol

In the case of the 14β,17β-propeno bridged compound **119** the introduction of unsaturation also flattens the bridging ring. A possible explanation for the dramatic loss of binding affinity (relative to **116**) is that the slightly altered orientation of C-17^2 places it in an extremely unfavourable position, which results in a destabilisation of the receptor-ligand interaction (Figure 4.10).

Figure 4.10: Superimposition of 14β,17β-propeno derivative **119** with estradiol

From this brief examination of structures, it has been concluded that the estradiol receptor is able to accommodate 'linear' steric bulk on the α-face of ring D. This corresponds with the results discussed in the introduction related to the methylation of estradiol, where substitution at the 17α- position was not detrimental to binding. The complete loss of activity for the 14β,17β-propano and 14β,17β-propeno bridged compounds (**116** and **119**) could be due to a number of factors. The first possibility is the poor alignment of the 17α-hydroxy relative to estradiol, with this group possibly protruding into a hydrophobic region of the receptor; alternatively it could be that the extra steric bulk introduced on the β-face of the molecule prevents binding due to close contacts with an inflexible portion of the receptor.

In an attempt to explain the difference in binding affinity between the 14α,17α-bridged compounds and the 14β,17β-bridged compounds, estradiol, 14α,17α-ethano 3,17β-diol **60**, 14α,17α-propano 3,17β-diol **114** and 14β,17β-propano 3,17α-diol **116** were superimposed. Then the van der Waals volume occupied by the active analogues (estradiol, **60** and **114**) was subtracted from the volume occupied by the inactive analogue **116**. The volume remaining must therefore be the portion of **116** responsible for the loss of binding affinity. Three different views of this volume superimposed on the structure of **116** are displayed in Figure 4.11.

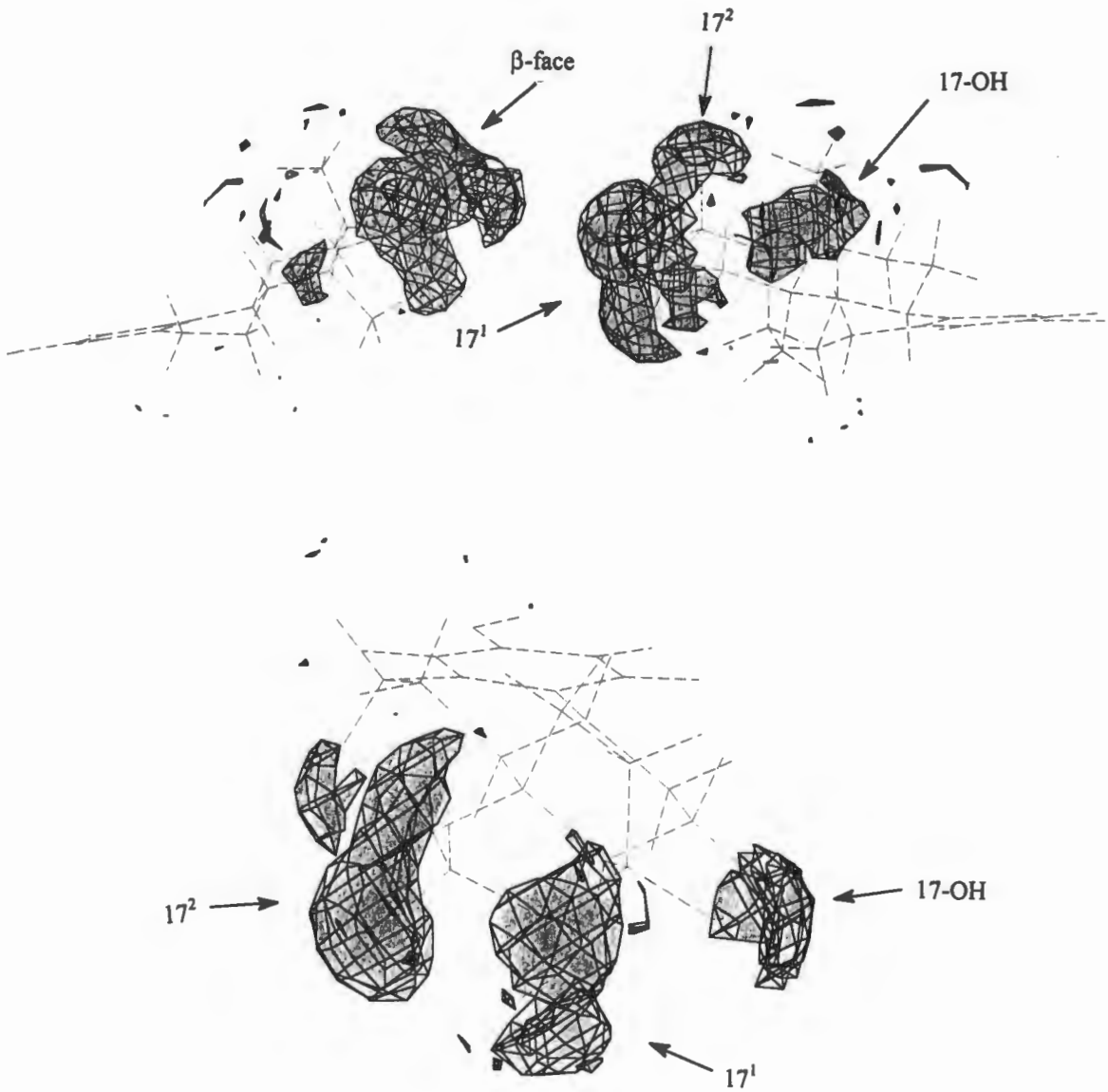


Figure 4.11: Three views of the additional steric bulk associated with the 14β,17β-propano derivative **116**

As can be seen from Figure 4.11, this extra steric bulk is largely located on the β-face of ring D. The main areas of difference are the orientation of the 17-hydroxy group, the 17^1-carbon and the 17^2-carbon. This leads to the preliminary conclusion that the observed loss of binding affinity is probably due to a combination of the misaligned 17-hydroxy group and the additional steric hindrance imposed by the 14β,17β-propano bridge.

The next series of compounds to be investigated were the 14,16-bridged estradiol analogues **120-125**. [14,16β-ethano-14β-estra-1,3,5(10)-triene-3,17β-diol **120** and 14,16β-ethano-14β-estra-1,3,5(10)-triene-3,17α-diol **123**, [90] 14,16α-ethanoestra-1,3,5(10)-triene-3,17β-diol **121** and 14,16α-ethanoestra-1,3,5(10)-triene-3,17α-diol **124**, [32] 14,17α-ethano-17a-homoestra-1,3,5(10)-triene-3,17β-diol **122** and 14,17α-ethano-17a-homoestra-1,3,5(10)-triene-3,17α-diol **125**] [34] The structures of these compounds along with their binding affinity are displayed in Figure 4.12. For simplicity, only the ring D portion of each compound has been shown.

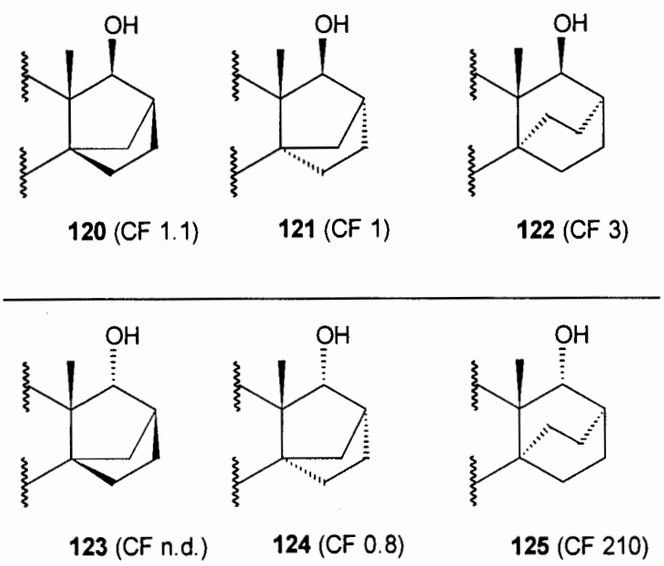


Figure 4.12: 14,16-Bridged estradiol analogues **120-125** (n.d. = not determined)

These analogues can be divided into a 17β-series (**120-122**) and a 17α-series (**123-125**). In the case of **122** and **125** the correct nomenclature is actually 17aβ and 17aα, but for the purpose of this discussion they will be classified as 17β and 17α compounds respectively.

Considering the 17β-series first, it is evident from the superimpositions with estradiol (Figure 4.13) that all three have structures very similar to that of estradiol.

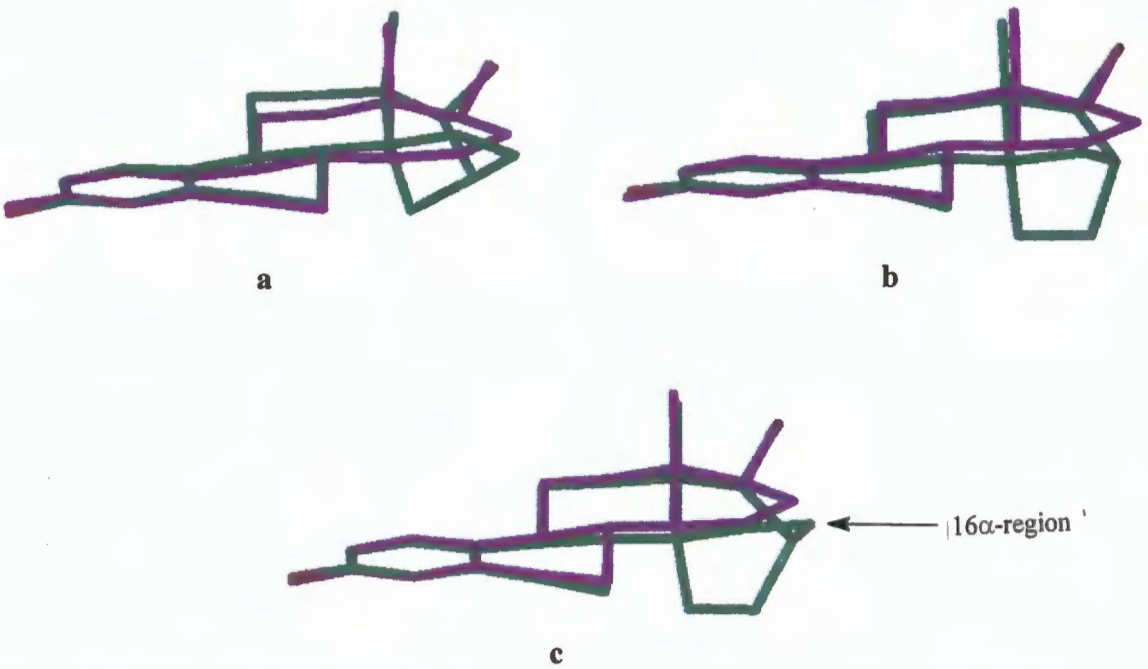


Figure 4.13: (a) Superimposition of 14β,16β-ethano compound **120** with estradiol, (b) superimposition of 14α,16α-ethano derivative **121** with estradiol, (c) superimposition of 14α,17α-ethano 17a-homo analogue **122** with estradiol

From the observed binding affinities, it appears as though the receptor is able to accommodate the 14α,16α-bridge readily, and apart from this, the two 14,16-ethano bridged compounds, **120** and **121**, do not introduce any other significant steric bulk. On the other hand, the 14α,17α-ethano 17a-homo derivative, **122** does introduce some steric bulk in the 16α-region (indicated on Figure 4.13, **c**). This could be the reason for the slight loss of activity observed in this case.

In the 17α-series, all of the molecules have the 17-hydroxy group in the 17α-orientation, which is expected to be deactivating towards receptor binding. While this holds true for the 14α,17α-ethano 17a-homo compound **125**, it is clearly not the case for the 14α,16α-ethano compound **124**. The corresponding 14β,16β-ethano compound **123** has not been synthesised as yet, and so cannot be included in this comparison.

From the superimpositions with estradiol (Figure 4.14), it is evident that none of these compounds fit the template (estradiol) very well. In order to accommodate the misaligned 17-hydroxy group, a significant distortion of the backbone is required. The superimpositions of the two compounds which have been synthesised, **124** and **125**, will be discussed further.

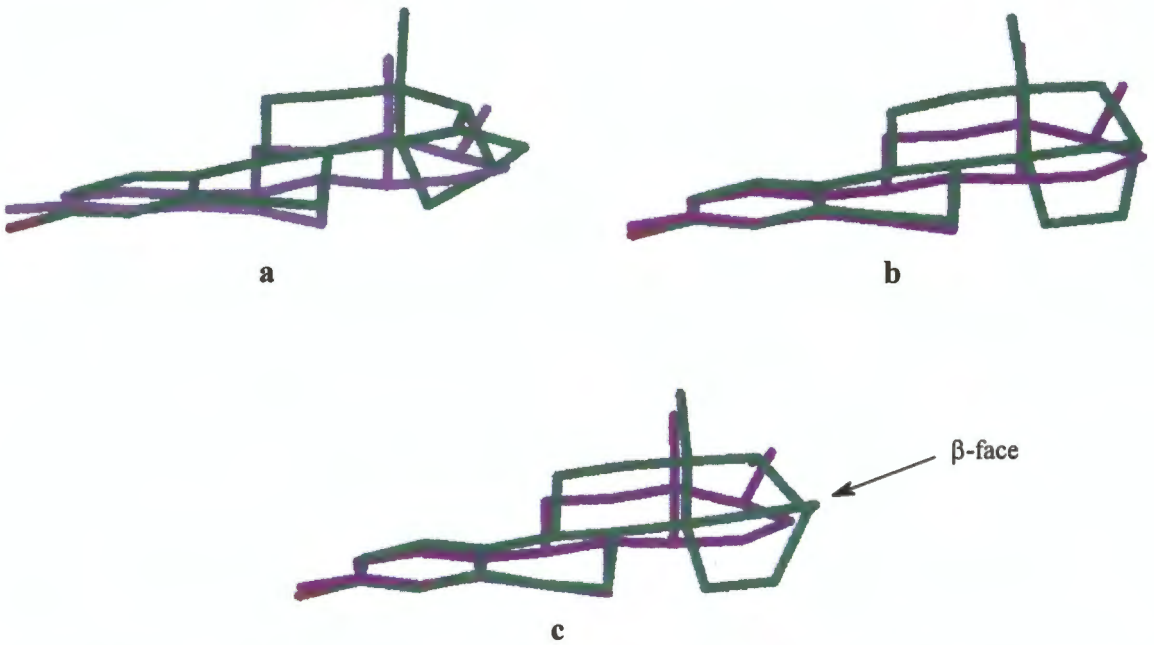


Figure 4.14: (a) Superimposition of 14β,16β-ethano derivative **123** with estradiol, (b) superimposition of 14α,16α-ethano compound **124** with estradiol, (c) superimposition of 14α,17α-ethano 17a-homo derivative **125** with estradiol

Considering the 14α,16α-ethano compound **124**, from the superimposition with estradiol (Figure 4.14, **b**) it would appear as though the receptor is capable of recognising structures with a 17α-hydroxy group. Possibly the lack of steric bulk on the β-face (unlike the 14β,17β-propano compound **116**) and the presence of steric bulk on the α-face of the molecule (unlike estra-1,3,5(10)-triene-3,17α-diol) [25] prevents this group from deactivating the molecule towards receptor binding.

The 17a-homo compound, **125** has a low binding affinity, which can be explained as being due to a combination of the misaligned 17-hydroxy group and the steric bulk introduced on the β-face, similar to the explanation for the 14β,17β-propano compound **116**. Thus it

would appear as though **both** an incorrectly oriented 17-hydroxy group and steric bulk on the β-face are required for the loss of binding affinity. On this basis, the 14β,16β-ethano analogue **123** is an extremely interesting synthetic target, as it has the incorrectly oriented 17-hydroxy group, along with steric bulk on the β-face, and provides an excellent candidate to test the validity of this hypothesis.

Further support for this proposal is obtained from another series of compounds, the 14β,15β-cycloalka analogues **126-131** (Figure 4.15). {cyclobuta[14,15]-14β-estra-1,3,5(10)-triene-3,17β-diol **126** and cyclobuta[14,15]-14β-estra-1,3,5(10)-triene-3,17α-diol **129**, [36] cyclopenta[14,15]-14β-estra-1,3,5(10)-triene-3,17β-diol **127** and cyclopenta[14,15]-14β-estra-1,3,5(10)-triene-3,17α-diol **130**, [37] perhydrobenzo-14β-estra-1,3,5(10)-triene-3,17β-diol **128** and perhydrobenzo-14β-estra-1,3,5(10)-triene-3,17α-diol **131**} [40]

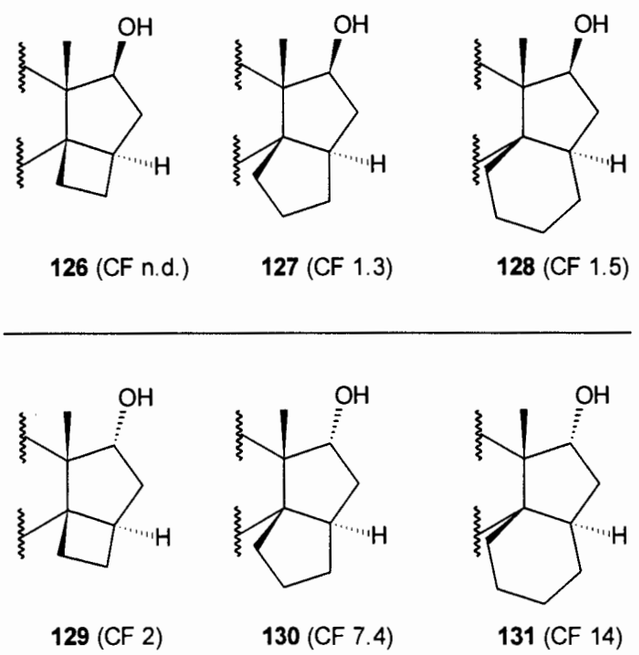
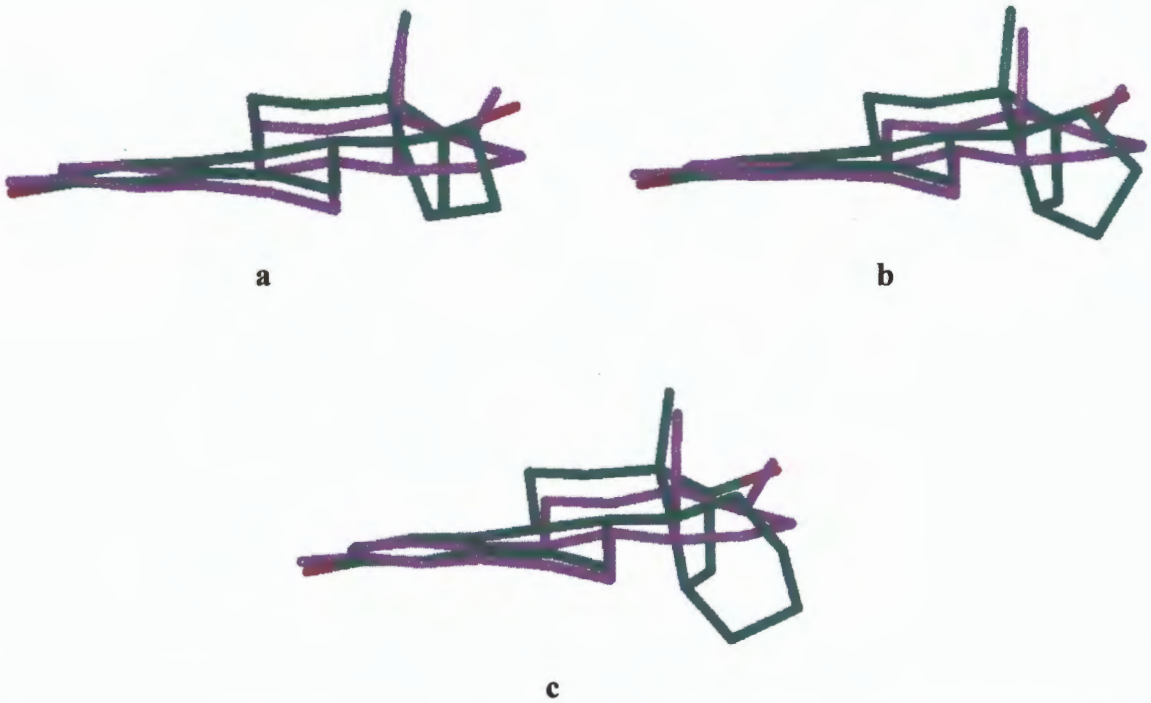


Figure 4.15: 14β,15β-Cycloalka analogues of estradiol **126-131**

Once again, these compounds can be grouped into a 17α- and a 17β-series. In the 17β-series binding affinities have been determined only for the cyclopenta[14β,15β] **127**

and the perhydrobenzo-14β **128** analogues. Both of these analogues display a fairly significant deviation relative to estradiol upon superimposition (Figure 4.16).



a **b**

c

Figure 4.16: (a) Superimposition of cyclobuta[14β,15β] analogue **126** with estradiol, (b) superimposition of cyclopenta[14β,15β] compound **127** with estradiol, (c) superimposition of perhydrobenzo-14β analogue **128** with estradiol

From the observed high binding affinities for the cyclopenta[14β,15β] **127** and perhydrobenzo-14β **128** analogues it can be concluded that the receptor is capable of accommodating steric bulk on the α-face, in the 14α,15α-region (relative to estradiol). This agrees with the previous findings that steric bulk on the α-face (relative to ring D of estradiol) is not detrimental towards receptor binding. On this basis, it is anticipated that the cyclobuta[14β,15β] analogue **126** will display significant binding affinity.

The corresponding 17α-series displays a similar pattern of poor superimpositions with estradiol (Figure 4.17). Although the cyclobuta[14β,15β] analogue **129** has a 17α-hydroxy group, the presence of steric bulk in the α-face region of ring D (relative to estradiol, as indicated on Figure 4.17, **a**) appears to reduce the negative impact of this misaligned

functional group. This explanation is similar to that proposed for the 14α,16α-ethano compound **124**, and the molecule displays significant binding affinity.

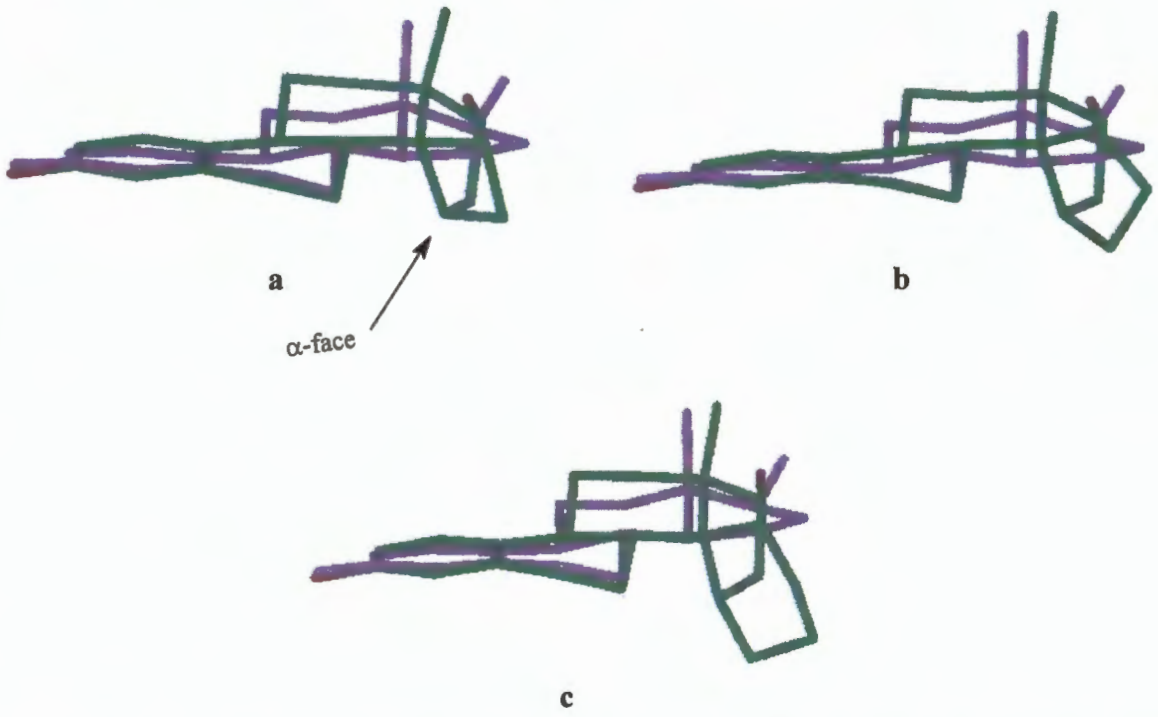
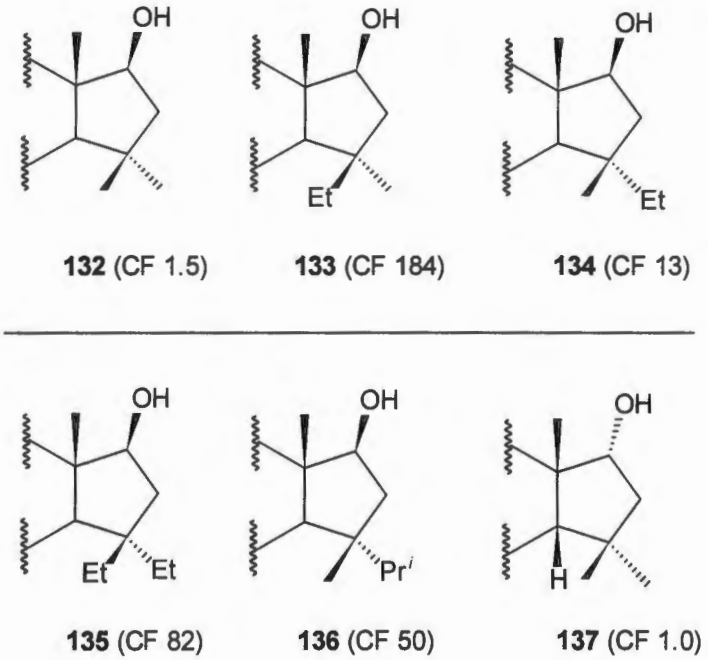


Figure 4.17: (a) Superimposition of cyclobuta[14β,15β] analogue **129** with estradiol, (b) superimposition of cyclopenta[14β,15β] compound **130** with estradiol, (c) superimposition of perhydrobenzo 14β-analogue **131** with estradiol

As the size of the 14β,15β-ring increases, the binding affinity decreases. As is evident from the superimpositions of the cyclopenta[14β,15β] **130** and the perhydrobenzo 14β **131** compounds, increasing the size of this ring has little effect on the remainder of the molecule. Thus, the reduction in binding affinity must be due to the increased steric bulk destabilising the receptor-ligand interaction.

Another important class of compounds to be studied are the 15,15-dialkyl analogues **132-137** (Figure 4.18). [66] Apart from the 14β-analogue **137**, all of these compounds have very similar conformations, however for those possessing longer alkyl chains (ethyl, isopropyl) the possibility of rotamers exists. As the energy barrier between these forms is likely to be small (i.e. relatively free rotation), only the lowest energy form of each compound has been considered in the superimpositional study.



132 (CF 1.5) **133** (CF 184) **134** (CF 13)

135 (CF 82) **136** (CF 50) **137** (CF 1.0)

Figure 4.18: 15,15-Dialkyl estradiol analogues **132-137**

Immediately evident from the biological results is that the introduction of the 15,15-dimethyl groups does not significantly impede binding. This is a surprising observation in the light of the reported poor binding affinity displayed by the corresponding 15β-methyl and 15α-methyl analogues. [26] Modelling indicates that the steric demand of the 15,15-dimethyl analogue is simply the sum of the 15β-methyl and 15α-methyl analogues; hence the combination of methyl groups must impart some additional stability to the receptor-ligand complex. From the superimposition of the 15,15-dimethyl analogue **132** with estradiol (Figure 4.19), it is evident that the only substantial difference between the two molecules is the two methyl groups at C-15. Hence it can be concluded that the receptor is capable of accommodating this steric bulk in a 17β-derivative.

Figure 4.19: Superimposition of the 15,15-dimethyl analogue **132** with estradiol

If the alkyl chains at either C-15α or C-15β are extended, then binding affinity decreases sharply. In the superimpositions of the four chain extended analogues, **133-136**, with estradiol (Figure 4.20) no significant deviations relative to estradiol are observed, so this loss of binding affinity must be due to the increased steric bulk in either the 15α- or 15β-regions (or both).

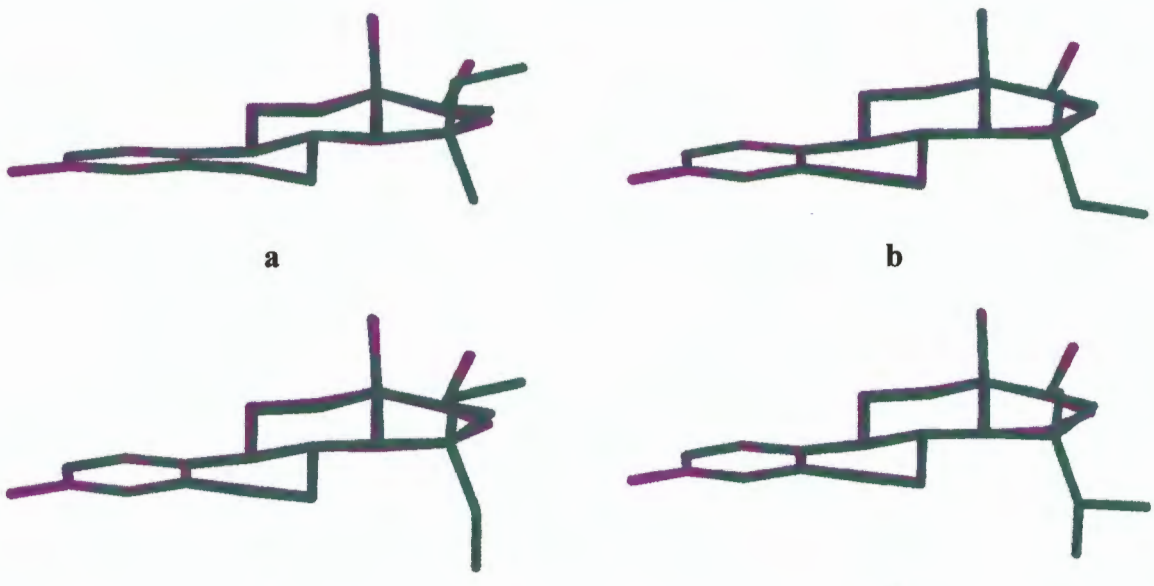


Figure 4.20: (a) Superimposition of 15β-ethyl-15α-methyl derivative **133** with estradiol, (b) superimposition of 15α-ethyl-15β-methyl analogue **134** with estradiol, (c) superimposition of 15,15-diethyl compound **135** with estradiol, (d) superimposition of 15α-*iso*-propyl-15β-methyl analogue **136** with estradiol

The binding results appear to indicate that the receptor is better able to accommodate steric bulk on the α-face than on the β-face, as the loss of activity on extension of the 15β-alkyl chain is more pronounced.

The 15,15-dimethyl 14β analogue **137** can be classified as a member of the 17α-series, and displays similar characteristics to other compounds in this series mentioned previously. Despite the poor overlap with estradiol displayed in the superimposition (Figure 4.21), and the incorrectly oriented 17-hydroxy group, this molecule retains binding affinity. This can once again be ascribed to the fact that there is steric bulk on the α-face of the molecule

(relative to the estradiol template), and no steric bulk on the β-face. Thus this molecule fits in with the previously identified pattern of binding for 17α-analogues.

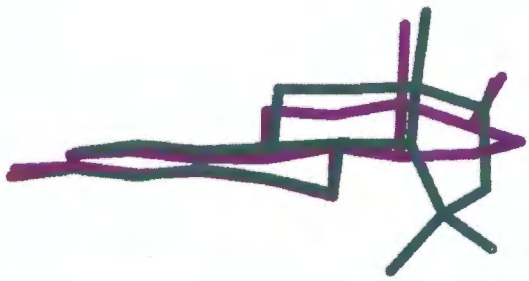


Figure 4.21: Superimposition of the 15,15-dimethyl 14β-analogue **137** with estradiol

From this brief investigation of ring D modified estradiol analogues, it appears as though the selected mode of superimposition is a reasonable first method with which to evaluate estradiol analogues. On this basis, a picture has begun to emerge regarding the nature of the steric environment surrounding the ring D region. It appears as though there is a pocket located on the α-face (relative to estradiol) which is able to accommodate small groups without a loss of binding affinity, and in some cases with enhanced affinity.

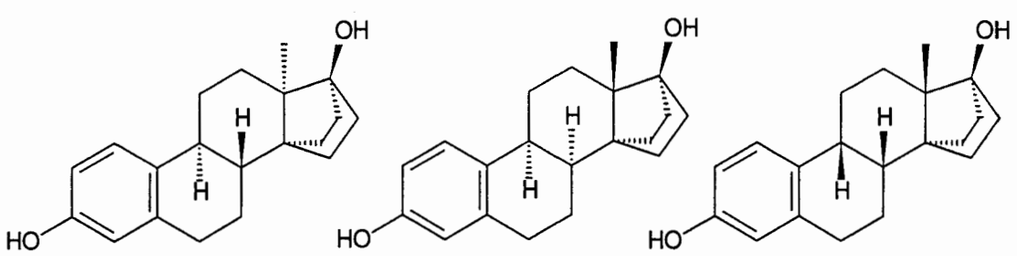
Surprisingly, the orientation of the 17-hydroxy group is not as critical as originally supposed. It appears as though the presence of steric bulk on the α-face (relative to estradiol) reduces the negative impact that a 17α-hydroxy group otherwise introduces. However, the combination of a 17α-hydroxy group and steric bulk on the β-face (relative to estradiol) leads to a complete loss of binding affinity.

The synthetic targets investigated in this thesis were then examined using this preliminary hypothesis as the basis for making qualitative predictions of activity. The skeletally modified analogues will be considered first, followed by the 15,17-bridged compounds.

4.3 Predictive modelling studies

4.3.1 Skeletally modified analogues of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol

Unlike all the previously discussed estradiol analogues, the skeletally modified estradiol analogues (**138**, **26** and **68**, Figure 4.22) are incapable of adopting the ring B half-chair ($^{8}H_{7}$), ring C chair ($^{8}C_{12}$) conformation that is invariably the lowest energy conformation in the natural series. Furthermore, the conformational flexibility of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol **60** (as determined by the molecular dynamics simulation) is not in any way representative of the flexibility of these molecules. Thus, a conformational search was conducted on each of these skeletally modified 14α,17α-ethanoestradiol analogues to determine the global minimum energy structure. Molecular dynamics simulations were then performed in order to ascertain the relative flexibility of these analogues. Table 4.4 summarises the results of the conformational search, the results for **60** have been included for comparison purposes. In the case of the 9β-analogue **68**, four conformations were identified, and these have all been included, in order of steric energy.



138 (CF n.d.) **26** (CF 2.2) **68** (CF 7.9)

Figure 4.22: Skeletally modified 14α,17α-ethano estradiol analogues **138**, **26** and **68**

Table 4.26: Selected torsion angles, interatomic distances and puckering parameters [178, 179] for the low energy conformations of 14,17α-ethano-8ξ,9ξ,13ξ-estra-1,3,5(10)-trien-17β-ols. Minimum energy conformations are indicated in bold type.

			Ring B					Ring C			
Cpd.	E/kcal mol^{-1} *	Conf.	ϕ_1° **	Q/Å	ϕ°	θ°	Conf.	ϕ_2° ***	Q/Å	ϕ°	θ°
60	87.8	^{8}**H$_7$**	-60.2	0.488	26.4	134.5	^{8}**C$_{12}$**	48.6	0.547	283.1	4.8
138	107.1	^{8}**E**	-60.1	0.518	4.9	133.9	^{14}**T$_9$**	54.2	0.665	78.5	89.0
26	99.9	^{7}**H$_8$**	56.5	0.458	207.7	44.7	^{8}**C$_{12}$**	49.4	0.522	205.7	4.0
68a	93.0	^{7}**H$_8$**	54.4	0.439	200.8	44.8	^{8}**C$_{12}$**	54.4	0.542	259.4	6.9
68b	93.9	^{6,9}**B**	-4.7	0.601	116.1	90.4	^{8}**C$_{12}$**	45.4	0.528	246.2	8.1
68c	98.2	E_7	-50.8	0.434	57.2	130.0	$^{9}T_{14}$	-53.5	0.680	267.6	88.4
68d	99.8	$^{7}S_{\ell}$	30.5	0.504	275.7	73.4	$^{9}T_{14}$	-46.5	0.640	274.4	84.7

* Steric energy as determined by CVFF [183]

** ϕ_1 = torsion angle defined by C6-C7-C8-C9 ($\phi_{6,7,8,9}$)

*** ϕ_2 = torsion angle defined by C8-C9-C11-C12 ($\phi_{8,9,11,12}$)

The conformational search performed on the 14α,17α-ethano 13α-derivative **138** indicated that the ^{8}E (envelope) ring B, $^{14}T_9$ (twist) ring C conformation has the lowest energy. The molecular dynamics simulation, performed as before, with the same two angles monitored throughout the simulation [$\phi_{6,7,8,9}$ (ϕ_1) and $\phi_{8,9,11,12}$ (ϕ_2)] (Figure 4.23) clearly showed the relative flexibility of both ring B and ring C.

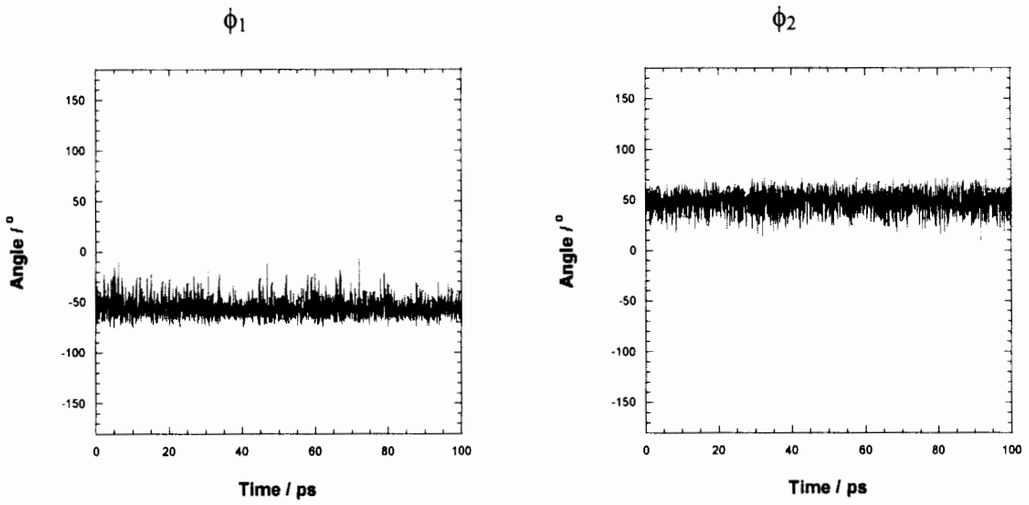


Figure 4.23: Results of the molecular dynamics simulation of the 14α,17α-ethano 13α analogue **138**. ϕ_1 ($\phi_{6,7,8,9}$) Indicates the relative flexibility of ring B, and ϕ_2 ($\phi_{8,9,11,12}$) that of ring C.

Analysis of the results shows that ϕ_1 varies from -60° to 0°, indicating that ring B is inverting from the ^8E to the $B_{6,9}$ conformation. However, the transient nature of this configuration is evident from the rapid reversion to the more stable ground state conformation. The flexibility of ring C is indicated by the variation of ϕ_2 which fluctuates between 60° and 10°, indicating that ring C is capable of undergoing interconversion from the $^{14}T_9$ (ground state) to other boat and twist conformations which cannot be identified from this parameter alone. However, the greater stability of the ground state conformation is again indicated by the transient nature of these other structures, which rapidly revert to the more stable form.

From the superimposition with estradiol (Figure 4.24), using the hypothesis developed, it is predicted that this analogue would be inactive. Firstly, the 17-hydroxy group is slightly misaligned, and secondly there is steric bulk on the β-face (relative to estradiol); the two factors that appear to cause a loss of binding affinity. However, the steric bulk on the β-face is in a different region to that identified as being detrimental to binding. In addition, the role of the 13α-methyl group has not been included in this prediction, and this could

introduce other factors influencing the receptor affinity. As this molecule has yet to be synthesised, this prediction cannot be verified.

Figure 4.24: Superimposition of the 14α,17α-ethano 13α analogue **138** with estradiol

The minimum energy structure determined for the 8α-analogue **26**, has the ring B half-chair ($^{7}H_{8}$), ring C chair ($^{8}C_{12}$) conformation. Although there is a *cis* fusion between rings B and C, the molecule is not very flexible as is indicated by the molecular dynamics study (Figure 4.25).

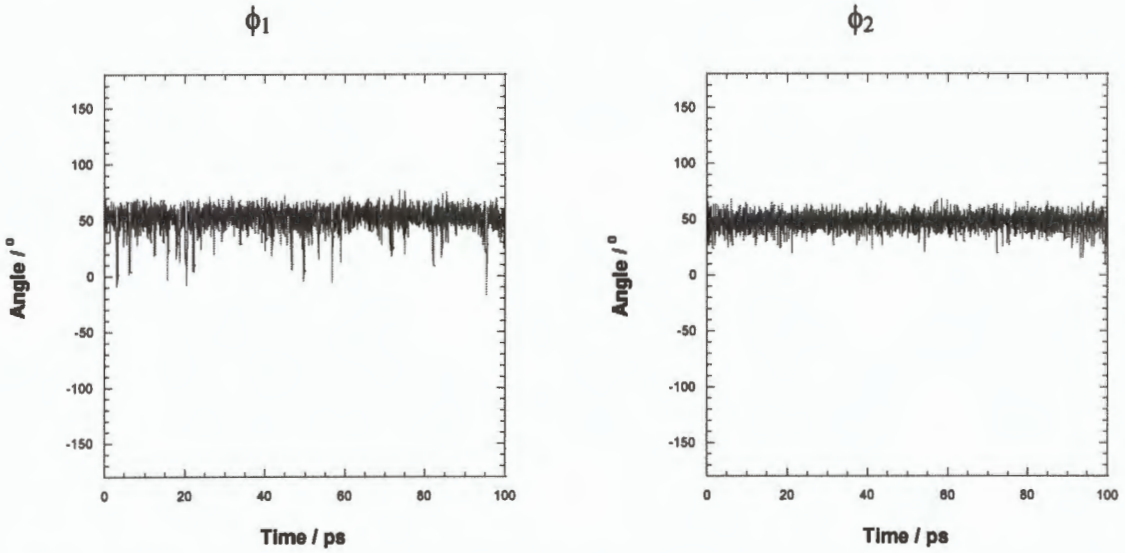


Figure 4.25: Results of the molecular dynamics simulation of the 14α,17α-ethano 8α derivative **26**. ϕ_1 ($\phi_{6,7,8,9}$) Indicates the relative flexibility of ring B, and ϕ_2 ($\phi_{8,9,11,12}$) that of ring C.

As can be seen from Figure 4.25, ϕ_1 varies from 60° to 0°, indicating that ring B undergoes inversion from the $^{7}H_{8}$ to the $^{6,9}B$ conformation. However, the molecule rapidly reverts to the lower energy 'ground state' conformation. Ring C does not undergo any inversion, as ϕ_2 remains at about 45°, indicative of the $^{8}C_{12}$ configuration.

Superimposition with estradiol (Figure 4.26) indicates that a reasonable overlap is achieved at the two polar ends of the molecule (3 and 17) and the extra steric bulk of ring D is situated on the α-face relative to estradiol. Thus, as there appear to be no obvious steric factors (of the nature discussed previously) impeding binding, it was anticipated that this analogue would display binding affinity.

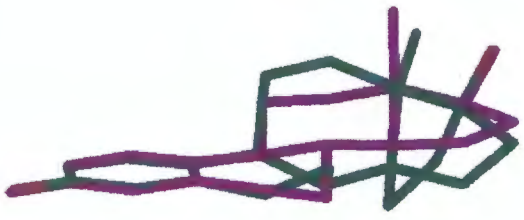


Figure 4.26: Superimposition of the 14α,17α-ethano 8α analogue **26** with estradiol

This expectation was borne out by the observed binding affinity (CF 2.2). The loss of affinity in comparison to the corresponding analogue in the natural series, **60**, is probably due to the poor alignment of rings B and C relative to estradiol. This slight loss of affinity on inversion at C-8 has also been observed in other estradiol analogues. [48, 49, 52]

Unlike the previous conformational searches, four conformations were identified for the 9β-analogue **68**. The relative steric energies of two of these are extremely close, so it is not possible to predict the favoured conformer. Both of these structures have ring C in the $^{8}C_{12}$ conformation, but they differ in ring B, which is either in the $^{7}H_{8}$ or the $^{6,9}B$ configuration. The other two structures, which are slightly higher in energy, have ring C in the $^{9}T_{14}$ form, and again differ in ring B, which is in either the E_{7} or the $^{7}S_{6}$ conformation. Perspective views of all four conformers are shown in Figure 4.27.

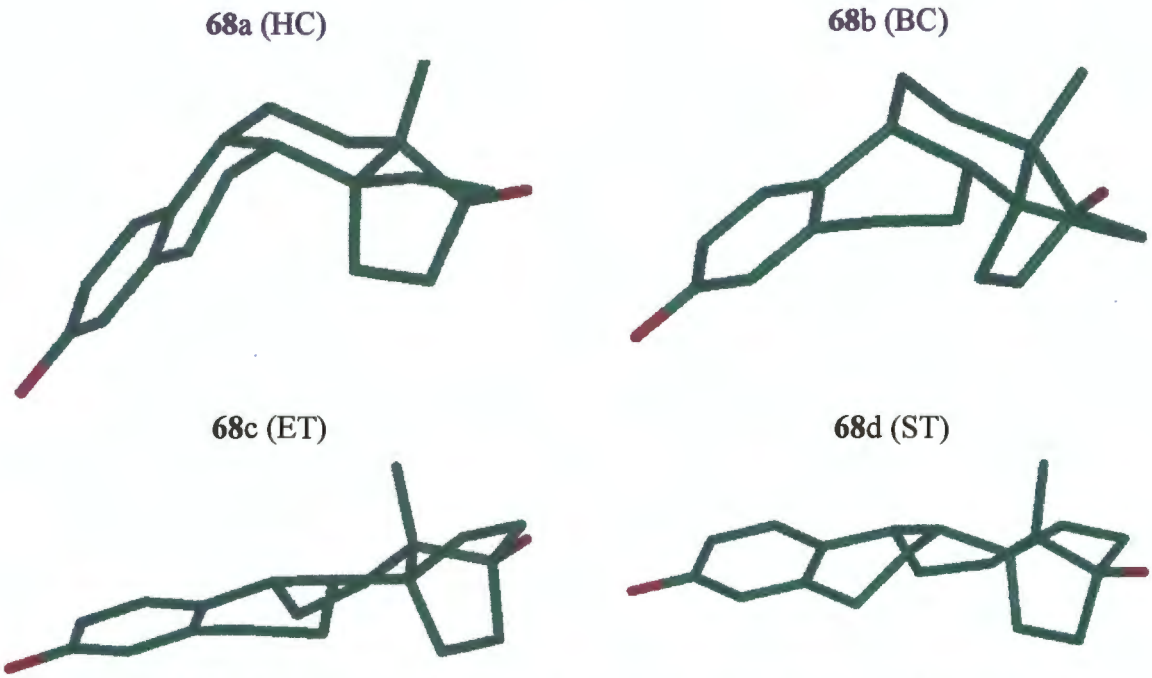


Figure 4.27: Perspective views of the four low energy conformations of the 9β-analogue **68**

The molecular dynamics simulation (performed on conformer **68a**) results (Figure 4.28) make the flexibility of ring B immediately apparent. Ring C, fairly rigid in all the previous molecules, appears to be substantially more flexible in this analogue.

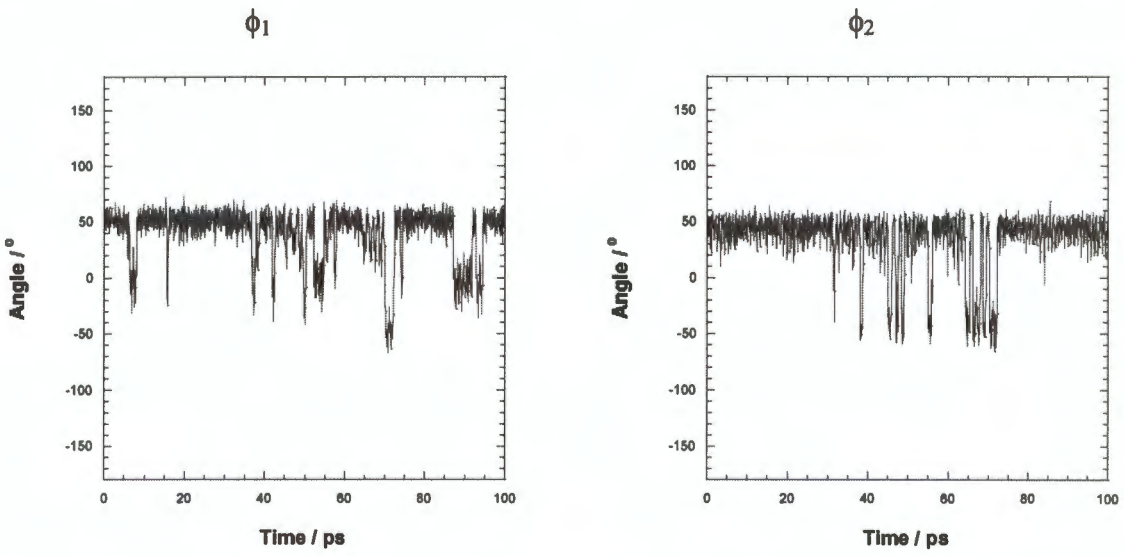


Figure 4.28: Results of the molecular dynamics simulation of the 9β-derivative **68a**. ϕ_1 ($\phi_{6,7,8,9}$) Indicates the relative flexibility of ring B, and ϕ_2 ($\phi_{8,9,11,12}$) that of ring C.

Analysis of the results indicates that ϕ_1 fluctuates from about 55° to -55° indicating that ring B varies from the starting $^{7}H_{8}$ conformation to the $^{6,9}B$ and other boat-like conformations. These other conformers appear to be fairly stable, as the molecule remains in these configurations for a significant time period before reverting to the alternative form. Ring C is more rigid, largely remaining in the $^{8}C_{12}$ conformation, as indicated by ϕ_2 which remains at about 55° for most of the simulation. Inversion of this ring is observed, however, for a significant percentage of the simulation, indicating that the higher energy conformers are accessible at 298K. Thus, as a significant amount of energy is released during the binding process (estimated to be -12.1 kcal mol^{-1})[27], the possibility exists that ring C might invert during binding, therefore these conformations must also be considered in the superimposition study.

All four conformations were superimposed with estradiol (Figure 4.29). It is apparent that the two lower energy conformers, with ring C in the chair conformation (**68**a and **68**b), are unlikely to possess significant affinity, as it is impossible to overlap ring A and the 17β-hydroxy group with the corresponding features of estradiol. Inversion of ring C, to produce conformers **68**c and **68**d improves the correlation, with conformer **68**c displaying a reasonable overlap with estradiol.

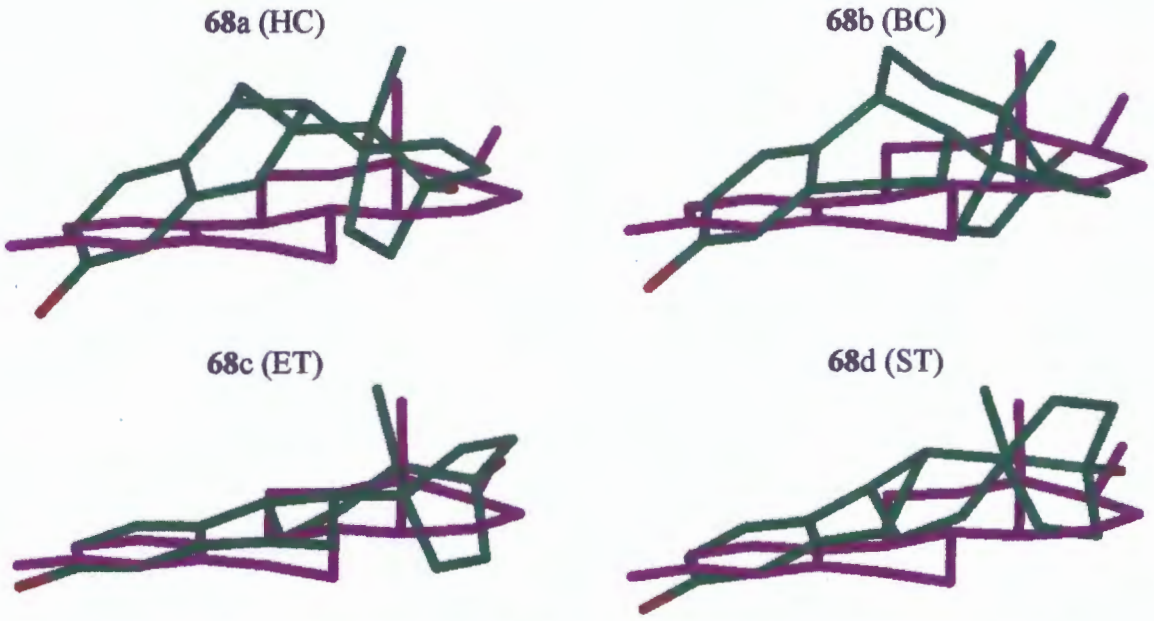
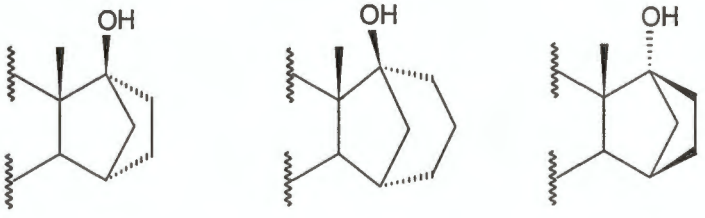


Figure 4.29: Superimpositions of the four low energy conformations of the 14α,17α-ethano 9β analogue **68**a-d with estradiol

In all previous cases, it has been assumed, based on the molecular dynamics simulations, that the minimum energy conformation is responsible for the observed binding affinity. In the case of this relatively flexible molecule, more than one structure could invoke a response. Hence, since conformer **68c** has the best overlap with estradiol, the predicted affinity will be based upon this superimposition. The 17-hydroxy group is in approximately the correct orientation and there is some steric bulk on the α-face. The presence of steric bulk on the β-face as well as the poor overlap of rings A, B and C is likely to counter this. On this basis, the 9β-analogue **68** is expected to display binding affinity, but it will probably be less active than the corresponding 'natural' analogue **60**. This expectation is borne out by the binding affinity (CF 7.9) substantially lower than the 'natural' analogue **60**.

4.3.2 Other estradiol analogues

The other synthetic targets to be investigated in this thesis were 15,17-bridged estradiol analogues. A small selection of these structures, indicated in Figure 4.30, will be presented in order to indicate their possible binding affinities. For simplicity only the ring D portion of the molecule is displayed.



139 **140** **141**

Figure 4.30: 15,17-bridged estradiol analogues **139-141**

It is apparent from their superimpositions with estradiol (Figure 4.31), that the 15α,17α-bridged analogues **139** and **140** display an extremely close correspondence to the template. The additional steric bulk introduced on the α-face should be readily accommodated by the receptor, thus it is anticipated that these two analogues will display high binding affinity. The 15β,17β-ethano analogue **141** possesses the two features

identified as having a negative impact on receptor binding, namely a 17α-hydroxy group and steric bulk on the β-face. Therefore, this analogue is not expected to be biologically active. As none of these targets has been synthesised as yet, these predictions can unfortunately not be verified.

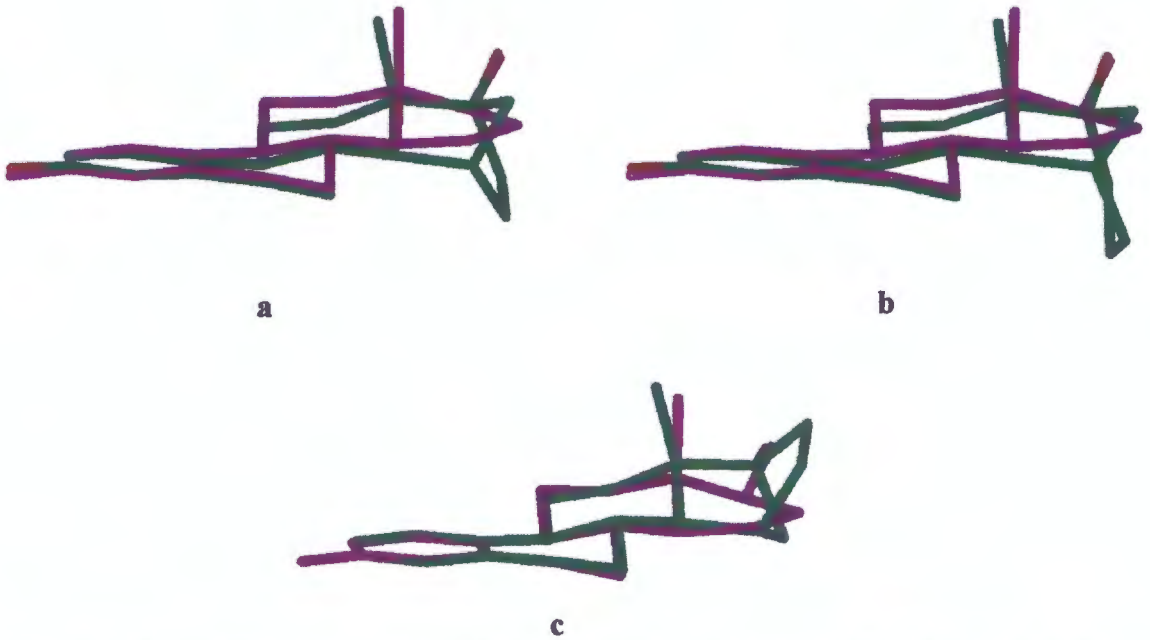


Figure 4.31: (a) Superimposition of 15α,17α-ethano analogue **139** with estradiol, (b) superimposition of 15α,17α-propano compound **140** with estradiol, (c) superimposition of 15β,17β-ethano analogue **141** with estradiol

Some other possible synthetic targets identified are the 14α,17aα-propano-17a-homo derivative **142** and the 14α,15α-cycloalka compounds **143-146** (Figure 4.32). The synthesis of these analogues has not been attempted in this thesis, but it was considered to be of interest to evaluate their binding affinities, based upon the model developed.

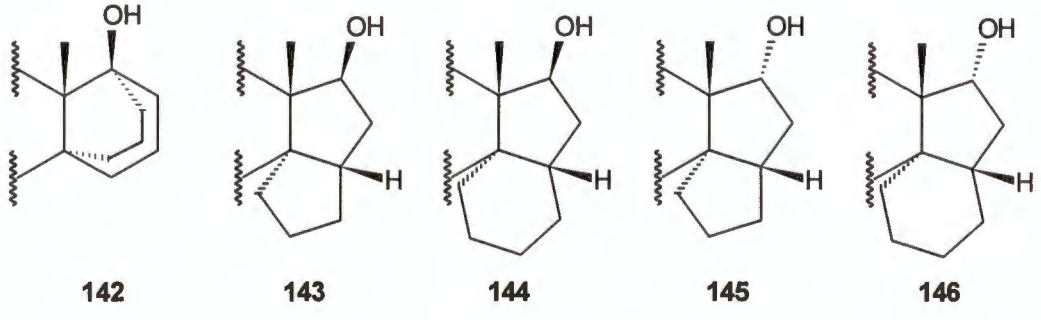


Figure 4.32: Other possible synthetic targets

On the basis of their superimpositions with estradiol, the 14α,15α-cycloalka compounds are all expected to display high binding affinity. Considering the 17β-compounds (**143** and **144**) first; the steric bulk on the α-face should be readily accommodated by the receptor, similarly to other derivatives discussed previously, and not impede receptor binding. As an example, Figure 4.33 shows the superimposition between the cyclopenta[14α,15α] compound **143** and estradiol. The 17α-compounds (**145** and **146**), have an unfavourably oriented 17-hydroxy group. However, they possess steric bulk on the α-face, which appears to reduce the negative impact of the 17α-hydroxy group, and hence these two derivatives are also expected to display high receptor affinity.

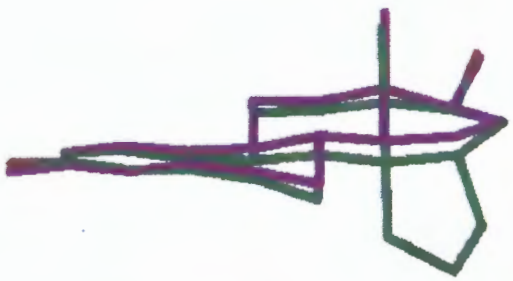


Figure 4.33: Superimposition of the cyclopenta[14α,15α] compound **143** with estradiol

The other compound, 14α,17aα-propano 17a-homo analogue **142** is an extremely interesting synthetic target. As can be seen from the superimposition with estradiol (Figure 4.34) the 17a-hydroxy group does not appear to be protruding into an unfavourable region of the receptor. However, **142** does possess steric bulk on the β-face (as indicated), which is linked with reduced binding affinity (in combination with a 17α-hydroxy group). These factors render it difficult to make a confident prediction regarding the affinity of this compound. This makes it an extremely appealing synthetic target.

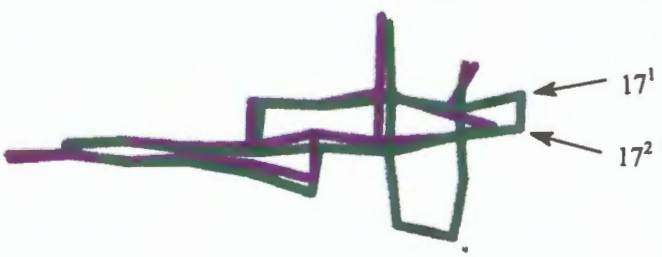


Figure 4.34: Superimposition of the 14α,17aα-propano 17a-homo compound **142** with estradiol

4.4 Receptor binding model based upon the observed structures

From an examination of the three X-ray crystal structure determinations conducted in this thesis, an alternative explanation based solely upon these data has also been developed. By superimposing the observed conformations upon that of estradiol (as observed in the estradiol-water crystal structure, [184] as this appears to be the most representative of the three crystal structures of estradiol that have been determined. For further details of this structure, see Appendix 5) using the same fitting procedure described previously (p. 117), the differences between the test molecules and the estradiol template can be readily ascertained. Any contradictions would necessitate a re-examination of the molecular modelling study and the conclusions drawn.

In the case of the 14α,17α-ethano compound **113**, two conformations were observed in the unit cell. From the superimpositions of each of these with estradiol (Figure 4.35), it is readily apparent that the only major difference is the presence of the 14α,17α-ethano bridge and the conformation of ring D, which is forced to adopt a highly puckered ^{13}E conformation in the 14α,17α-ethano compound.

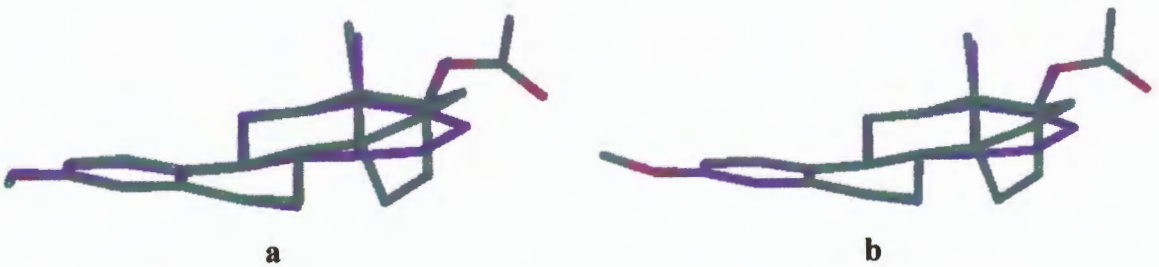
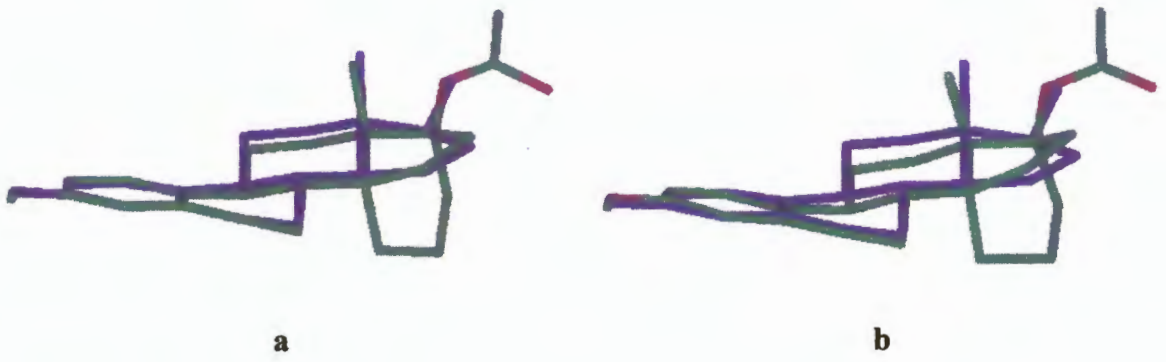


Figure 4.35: Superimposition of the 14α,17α-ethano compound **113** with estradiol. (**a**) Conformer A and (**b**) conformer B

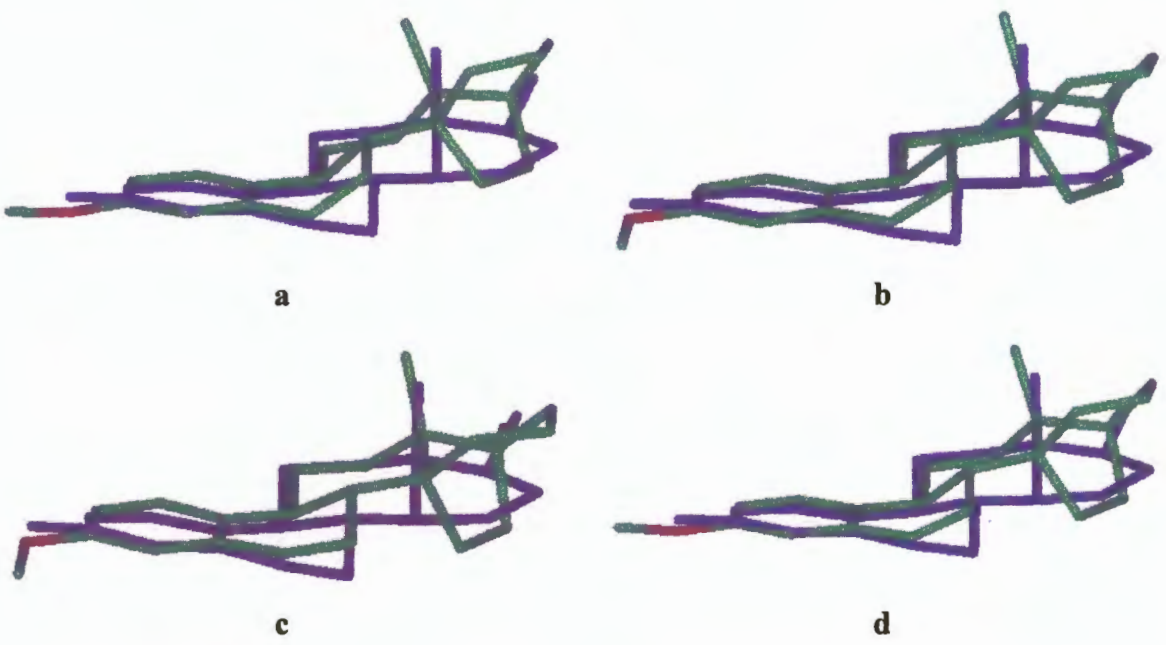
Similarly, in the case of the 14α,17α-propano compound **115**, the two conformations are fairly similar to estradiol (Figure 4.36), with one conformation having a somewhat poorer fit than the other. This is possibly due to the slight difference in the configuration of ring B and ring C, and serves to illustrate how slight differences in conformation of individual rings can result in rather different overall steric profiles.



a b

Figure 4.36: Superimposition of the 14α,17α-propano compound **115** with estradiol. (**a**) Conformer A and (**b**) conformer B

In the case of the 14β,17β-propano compound **117**, none of the observed conformations displays any significant overlap with estradiol (Figure 4.37). This is largely due to the different ring B conformation adopted by the estradiol analogue in the crystal structure (boat-like instead of the half-chair observed in estradiol).



a b

c d

Figure 4.37: Superimposition of the 14β,17β-propano compound **117** with estradiol. (**a**) Conformer A, (**b**) conformer B, (**c**) conformer C and (**d**) conformer D

From these superimpositions it appears as though the estradiol receptor is capable of accommodating steric bulk on the α-face of ring D, as has been concluded from the modelling study. However, in the case of the 14β,17β-propano compound **117**, the observed low binding affinity would appear to be due to the poor fit with estradiol.

The conclusions drawn from this crystallographic study are that α-face substitution on ring D, as well as a good fit with estradiol results in either enhanced or only slightly reduced receptor affinity. However, a poor fit with estradiol results in low receptor affinity. These do not in any way contradict the conclusions drawn from the modelling study and only provide further support for the developed hypothesis.

4.5 Conclusions

In the introduction to this chapter, two broad objectives were outlined, namely to explain the observed binding affinities and secondly to develop a basis for predicting the affinity of potential synthetic targets.

This investigation has succeeded in establishing a working hypothesis for interpreting the observed binding affinities. The method of superimposing the test molecule and estradiol appears to be a reasonable basis for comparison, and does provide a way of explaining the results obtained. However, this is largely an *a posteriori* interpretation, as it is not possible to quantify the effect that a novel structural modification will have on receptor binding affinity. Until the structure of the receptor before, during and after binding to the ligand can be determined, this will continue to be the case.

In an attempt to address the second objective, a large number of potential synthetic targets have been superimposed with estradiol and their activities predicted using the previously determined positive and negative structural features. While this approach has enabled the identification of possible synthetic targets, these predictions have, of necessity, been rather simple statements. It is not possible to predict actual binding affinities using this type of approach. Furthermore, as many of these targets have not yet been synthesised, correlation of predicted and observed activities is not possible. Thus, the second objective has been partially addressed, but there is scope for significant refinement of this approach.

Experimental

Melting points were measured using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter using chloroform solutions unless otherwise specified, and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in chloroform solutions using a Perkin-Elmer 983 infrared spectrometer or a Perkin-Elmer Paragon 1000 FT-IR spectrometer, over the range 4000-800 cm^{-1}. Microanalyses were determined using a Fisons EA 1108 CHNS-O instrument. Mass spectra were recorded on a VG micromass 16F spectrometer operating at 70 eV with an accelerating voltage of 4 kV and a variable source temperature (depending on the nature of the compound). Accurate masses were determined on a VG-70E spectrometer at the Cape Technikon. All ^{1}H-NMR spectra were recorded, unless otherwise specified, as deuteriochloroform solutions using tetramethylsilane as an internal standard on a Varian VXR-200 (200 MHz) or a Varian Unity Spectrometer (400 MHz). ^{13}C-NMR spectra were recorded on the same instruments at 50 or 100 MHz (using tetramethylsilane as an internal standard).

Thin layer chromatography was performed on aluminium backed silica gel 60 F_{254} plates in a variety of solvent systems using the ascending technique. The plates were visualised by spraying with cerium(IV) ammonium sulfate in 8 mol dm^{-3} sulfuric acid and baking at 200°C. Column chromatography was conducted with Merck Kieselgel 60: 70-230 mesh for gravity and 230-400 mesh for flash chromatography.

All solvents used were dried by the appropriate technique [185] and unless otherwise specified, all reactions were carried out under a nitrogen or argon atmosphere with exclusion of water and oxygen.

A list of abbreviations can be found in Appendix 3.

Computational results were obtained using software programs from Molecular Simulations [186] - dynamics calculations were done with the Discover ® program (version 2.9.8) using the CVFF forcefield.

Molecules were minimised using the Discover ® program (version 2.9.8) using the CVFF forcefield using a combination of steepest descents, conjugate gradient and modified Newton-Raphson minimisation techniques as implemented within the software. Superimpositions were performed using the superimpose command as implemented within the software.

Molecular dynamics simulations were performed using a constant volume, constant temperature (NVT) ensemble at 298K with the Verlet leapfrog integrator and a 1 fs timestep. An initial 10 ps equilibration period was followed by a 100 ps data collection period in which structures were sampled every 50 fs.

3-Methoxy-13α-estra-1,3,5(10)-trien-17-one 3

A solution of estrone 3-methyl ether **1** (13.5 g, 48 mmol), hydroxylamine hydrochloride (8.4 g, 120 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (3 g, 43 mmol) was refluxed in methanol (300 cm^3) for 2h. The methanol was removed under reduced pressure and the residue was dissolved in chloroform, washed [water, aq. HCl (1 mol dm^{-3}), satd. aq. $NaHCO_3$, water], dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a solid residue (16.7 g) which was dissolved in a mixture of pyridine (50 cm^3) and acetic anhydride (30 cm^3) and stirred at 25°C for 2 h. Water and solid sodium hydrogen carbonate were added until effervescence ceased. The precipitate was filtered off under suction, thoroughly washed with water and dried to give the crude oxime acetate **2** as a pale yellow solid (18 g) (*m/z* 341).

A solution of the oxime acetate **2** (2 g) was refluxed with nickel powder (2.5 g) in a mixture of acetic acid (50 cm^3) and hexane (50 cm^3) for 24 h. Water and solid sodium hydrogen carbonate were added to the cooled solution until effervescence ceased and the resulting mixture was extracted with ethyl acetate. This extract was washed (satd. aq. $NaHCO_3$, water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (1.19 g). One recrystallisation from methanol afforded pure 3-methoxy-13α-estra-1,3,5(10)-trien-17-one **3** (562 mg, 34%), m.p. 128-130°C; $[\alpha]_D$ -30° (*c* 0.8) (lit., [43, 44] 130-133°C; $[\alpha]_D$ -27.5°) (Found: C, 80.3; H, 8.65; M^+, 284. $C_{19}H_{24}O_2$ requires C, 80.2; H, 8.5; *M*, 284); ν_{max}/cm^{-1} 1728; δ_H (400 MHz) 0.92 (1H, qd, *J* 3 x 11 and 2.8 Hz, 8β-H), 0.98 (1H, m, 11β-H), 1.06 (3H, s, 13α-Me), 1.75 (1H, dd, *J* 11 and 6.1 Hz, 14α-H), 1.95 (1H, td, *J* 2 x 11.6 and 5.5 Hz, 15β-H), 2.83 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.9 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.9 Hz, 2-H) and 7.18 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 21.0 (C-15), 25.1 (13α-Me), 28.2 (C-11), 28.3 (C-7), 30.3 (C-6), 32.0 (C-12), 33.4 (C-16), 41.4 (C-9), 41.5 (C-8), 49.3 (C-14), 50.1 (C-13), 55.1 (3-OMe), 111.7 (C-2), 113.5 (C-4), 126.8 (C-1), 131.9 (C-10), 138.0 (C-5), 157.5 (C-3) and 210.0 (C-17). The mother liquor residue was adsorbed on silica gel (50 g) and eluted with ethyl acetate-hexane (1:9) to give further 13α-17-ketone **3** (284 mg, 17%) followed by estrone 3-methyl ether **1** (137 mg, 8%)

3-Methoxy-13α-estra-1,3,5(10),15-tetraen-17-one 4

A solution of the 17-ketone **3** (1.03 g, 3.6 mmol) in tetrahydrofuran (THF) (20 cm^3) was added to a solution of lithium diisopropylamide [prepared by adding *n*-butyllithium (2.5 mol dm^{-3} in hexanes; 6 cm^3; 15 mmol) to a solution of diisopropylamine (2 cm^3; 15.3 mmol) in THF (10 cm^3) at -10°C and stirring the mixture at this temperature for 15 min and then cooling the mixture to -78°C] at -78°C and the mixture was stirred at this temperature for 1h. Chlorotrimethylsilane (1.9 cm^3; 15 mmol) was added and the mixture was allowed to warm up to 25°C. Water was added and the resulting mixture was extracted into diethyl ether. The extract was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude residue (1.3 g) which was refluxed in acetonitrile (70 cm^3) with palladium acetate (820 mg, 3.65 mmol) for 5h. The cooled mixture was filtered through Celite, and, after removal of the solvent, the residue (1.24 g) was flash chromatographed on silica gel (85 g) with ethyl acetate-hexane (1:9) as eluent to give the 17-ketone **3** (345 mg, 33%) followed by the Δ^{15} 17-*ketone* **4** (387 mg, 38%), m.p. 66-68°C (from diisopropyl ether); $[\alpha]_D$ -81° (*c* 0.8) (Found: C, 80.7; H, 7.9%; M^+, 282. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.9%; *M*, 282); ν_{max}/cm^{-1} 1701; δ_H (400 MHz) 1.20 (3H, s, 13α-Me), 1.73 (1H, qd, *J* 3 x 11.6 and 2.8 Hz, 8β-H), 2.16 (1H, ddd, *J* 13.9, 9.3 and 7 Hz, 12α-H), 2.61 (1H, dtd, *J* 12.7, 2 x 3.8 and 2.8 Hz, 7β-H), 2.71 (1H, ddd, *J* 11.6, 2.6 and 1.6 Hz, 14α-H), 2.82-2.91 (1H, m, 11β-H), 3.01-3.09 (1H, m, 9α-H), 3.21 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 6.17 (1H, dd, *J* 5.8 and 1.6 Hz, 16-H), 6.58 (1H, d, *J* 2.8 Hz, 4-H), 6.73 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.13 (1H, dd, *J* 8.6 and 0.6 Hz, 1-H) and 7.76 (1H, dd, *J* 5.8 and 2.6 Hz, 15-H); δ_C (100 MHz) 24.2 (13α-Me), 27.0 (C-11), 28.2 (C-7), 29.2 (C-12), 29.9 (C-6), 38.4 (C-9), 41.2 (C-8), 46.5 (C-13), 55.2 (3-OMe), 56.7 (C-14), 112.3 (C-2), 113.3 (C-4), 128.0 (C-1), 131.3 (C-16), 132.8 (C-10), 137.2 (C-5), 157.4 (C-3), 164.0 (C-15) and 214.2 (C-17).

3-Methoxy-13α-estra-1,3,5(10),14,16-pentaen-17β-yl acetate 8

A solution of the Δ^{15} 17-ketone **4** (100 mg, 0.35 mmol) and toluene-*p*-sulfonic acid (20 mg) was refluxed in a mixture of acetic anhydride (5 cm^3) and isopropenyl acetate (5 cm^3) for 18h. The cooled solution was poured into saturated aqueous sodium hydrogen carbonate and extracted with diethyl ether. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude residue (650 mg) which was flash chromatographed on silica gel (20 g) with ethyl acetate-hexane (1:9) as eluent to give 3-methoxy-13α-estra-1,3,5(10),14,16-pentaen-17β-yl acetate **8** (10 mg; 9%) as an oil, *m/z* 324; δ_H (200 MHz) 1.11 (3H, s, 13α-Me), 2.23 (3H, s, 17-OC(O)C*H*$_3$), 3.79 (3H, s, 3-OMe), 5.85 (1H, m, 15-H), 6.17 (1H, d, *J* 2.3 Hz, 16-H), 6.68 (1H, d, *J* 2.5 Hz, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H) and 7.22 (1H, d, *J* 8.5 Hz, 1-H), followed by starting material **4** (80 mg; 80%).

Attempted formation of 17-trimethylsilyl-14,16-dienyl ether 9

Trimethylsilyltrifluoromethanesulfonate (1 cm^3, 5.2 mmol) was added to a solution of triethylamine (TEA) (0.8 cm^3, 5.7 mmol) in diethyl ether (2 cm^3) at 25°C and the mixture was stirred for 5 min. A solution of the Δ^{15} 17-ketone **4** (100 mg, 0.35 mmol) in diethyl ether (4 cm^3) was added and the resulting mixture was stirred at 25°C for 4h. Ice-water was then added and the resulting mixture was extracted into diethyl ether. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give an oily residue (70 mg) which was flash chromatographed on silica gel (20 g) with ethyl acetate-hexane (1:99) as eluent to give an oily residue (33 mg), which ^{1}H NMR analysis indicated was a complex mixture.

3-Methoxyestra-1,3,5(10),8,14-pentaen-17β-ol 11

A solution of the 3-methoxyestra-1,3,5(10),8,14-pentaene-17β-yl acetate **10** (660 mg, 2 mmol) in a mixture of THF (3 cm^3) and methanolic potassium hydroxide (1%; 20 cm^3) was stirred at 25°C for 90 min. Saturated aqueous ammonium chloride (25 cm^3) was added and the mixture was extracted into ethyl acetate. The combined organic phase was

washed (water, brine), dried ($MgSO_4$) and concentrated under reduced pressure to give the 17β-alcohol **11** (540 mg, 94%), m.p. 106-109°C (from ethanol) (lit., [69] 110-112°C), ν_{max}/cm^{-1} 3609 (OH); *m/z* 282; δ_H (200 MHz) 0.96 (3H, s, 13β-Me), 1.70, (1H, s, D_2O exch, 17β-OH), 3.80 (3H, s, 3-OMe), 4.10 (1H, dd, *J* 9.1 and 7.7 Hz, 17α-H), 5.50 (1H, t, *J* 2x2.9 Hz, 15-H), 6.70-6.79 (2H, m, 2- and 4-H) and 7.22 (1H, d, *J* 8.8 Hz, 1-H).

3-Methoxyestra-1,3,5(10),8,14-pentaen-17-one 12

A solution of the 17β-alcohol **11** (850 mg, 3.0 mmol), *N*-methylmorpholine (0.4 g) and crushed molecular sieves (4Å) in dry dichloromethane (15 cm^3) was stirred for 10 min at 25°C, then tetra-*n*-propylammonium perruthenate (TPAP) (35 mg, 0.1 mmol) was added and the mixture was stirred for 1h at 25°C. Dichloromethane (30 cm^3) was added and the resulting mixture was washed (satd. aq. Na_2SO_3, brine, satd. aq. $CuSO_4$), dried ($MgSO_4$) and evaporated to give a residue (1 g) which was adsorbed onto silica gel (80 g) and eluted with ethyl acetate-toluene (1:19) to give the 17-ketone **12** (169 mg, 20%), m.p. 136-142°C (lit., [79] 143°C); υ_{max}/cm^{-1} 1741 (C=O); *m/z* 280. Despite all attempts at purification, a persistent purple impurity remained in this material.

3-Methoxy-8α-estra-1,3,5(10)-trien-17-one 14

A solution of 3-methoxyestra-1,3,5(10),8,14-pentaen-17β-yl acetate **10** (8.6 g, 27 mmol) in ethanol (40 cm^3) was stirred with Raney nickel (Aldrich W-2; 5 cm^3) under a hydrogen atmosphere (50 bar) at 60°C for 48h. The mixture was filtered through Celite, and the catalyst was thoroughly washed with ethanol, ethyl acetate and chloroform. The filtrate was evaporated under reduced pressure to give a solid residue (10 g) [a portion of which was chromatographed on silica gel (10 g) with ethyl acetate-toluene (1:19) to give 3-methoxy-8α-estra-1,3,5(10)-trien-17β-yl acetate **13**, m.p. 97-99°C (from ethanol); $[\alpha]_D$ -10° (*c* 1.1) (lit., [48] 99°C; $[\alpha]_D$ -8.9°); *m/z* 328; ν_{max}/cm^{-1} 1720; δ_H (200 MHz) 0.92 (3H, s, 13β-Me), 2.05 (3H, s, 17β-OC(O)CH_3), 2.54-2.86 (3H, m, 6-H_2 and 9α-H), 3.77 (3H, s, 3-OMe), 4.63 (1H, dd, *J* 9.1 and 8.2 Hz, 17α-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.6 (1H, d, *J* 8.5 Hz, 1-H)].

The solid residue (9.9 g) was dissolved in a mixture of methanolic potassium hydroxide (1%, 60 cm^3) and THF (30 cm^3), and the mixture was stirred at 25°C for 18h. Water was added and the resulting mixture was extracted into ethyl acetate. The organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to afford a residue (7 g), which was dissolved in acetone (40 cm^3), cooled to 0°C and stirred vigorously while a solution of chromic acid (8 mol dm^{-3}, 10 cm^3, 27 mmol) was added. After stirring for 30 min at 0°C, water was added and the solution was extracted with ethyl acetate and chloroform. The combined organic extract was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude residue (7.17 g) which was flash chromatographed on silica gel (45 g), eluting with ethyl acetate-toluene (1:19) to afford 3-methoxy-8α-estra-1,3,5(10)-trien-17-one **14** (6.6 g, 87% from **10**), m.p. 89-90°C (from methanol); $[\alpha]_D$ +91° (*c* 2.9) (lit., [48] 93-94°C, $[\alpha]_D$ +100°); *m/z* 284; ν_{max}/cm^{-1} 1729; δ_H (400 MHz) 1.00 (3H, s, 13β-Me), 1.42 (1H, td, *J* 2 x 14.1 and 4.6 Hz, 12α-H), 2.48 (1H, ddd, *J* 19.0, 8.5 and 1.3 Hz, 16β-H), 2.62-2.74 (2H, m, 6α-H and 9α-H), 2.82 (1H, ddd, *J* 16.6, 4.9 and 2.0 Hz, 6β-H), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.05 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 16.2 (13β-Me), 21.4 (C-15), 21.6 (C-11), 28.5 (C-7), 31.4 (C-6), 32.3 (C-12), 35.7 (C-16), 38.7 (C-8), 41.2 (C-9), 47.1 (C-13), 48.7 (C-14), 55.2 (3-O*Me*), 112.2 (C-2), 113.3 (C-4), 130.2 (C-1), 133.3 (C-10), 137.5 (C-5), 157.4 (C-3) and 220.6 (C-17).

3-Methoxy-8α-estra-1,3,5(10),15-tetraen-17-one 15

A solution of the 17-ketone **14** (800 mg, 2.8 mmol) in THF (20 cm^3) was added to a solution of lithium diisopropylamide [prepared from *n*-butyllithium (2.5 mol dm^{-3} in hexanes, 6 cm^3, 15 mmol) and diisopropylamine (2 cm^3, 15.3 mmol) in THF (10 cm^3)] at -78°C and the mixture was stirred for 30 min. Chlorotrimethylsilane (1.9 cm^3, 15 mmol) was added and the mixture was stirred for 10 min and then allowed to warm up to 25°C. Saturated aqueous ammonium chloride was added and the resultant mixture was extracted into ethyl acetate. The combined organic phase was washed (water), dried ($MgSO_4$) and concentrated under reduced pressure to give a residue (1.2 g) which was refluxed with palladium acetate (670 mg, 3 mmol) in acetonitrile (70 cm^3) for 1h. The solids were filtered off, and the filtrate was evaporated under reduced pressure to give a solid residue

(1.01 g) which was flash chromatographed on silica gel (75 g) with toluene as eluent to afford the Δ^{15} 17-*ketone* **15** (795 mg, 100%), m.p. 115-116°C (from diisopropyl ether); $[\alpha]_D$ -39° (*c* 0.2) (Found: C, 81.0; H, 8.0%; M^+, 282. $C_{19}H_{22}O_2$ requires C, 80.8; H, 7.9%; *M*, 282); ν_{max}/cm^{-1} 1707 (C=O); δ_H (400 MHz) 1.24 (3H, s, 13β-Me), 2.41 (1H, m, 8α-H), 2.66-2.85 (3H, m, 6-H_2 and 9α-H), 2.97 (1H, m, $W_{½}$ 8Hz, 14α-H), 3.77 (3H, s, 3-OMe), 6.09 (1H, dd, *J* 6.0 and 3.4 Hz, 16-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H), 7.08 (1H, d, *J* 8.4 Hz, 1-H) and 7.59 (1H, ddd, *J* 6.0, 2.0 and 0.6 Hz, 15-H); δ_C (100 MHz) 22.8 (C-7), 23.3 (13β-Me), 28.5 (C-11), 30.3 (C-12), 31.6 (C-6), 37.8 (C-8), 40.8 (C-9), 52.0 (C-13), 54.0 (C-14), 55.2 (3-O*Me*), 112.3 (C-2), 113.5 (C-4), 130.1 (C-1), 131.9 (C-16), 132.9 (C-10), 137.4 (C-5), 157.5 (C-3), 160.4 (C-15) and 212.8 (C-17)

3-Methoxy-8α-estra-1,3,5(10),14,16-pentaen-17β-yl acetate 16

A solution of the Δ^{15} 17-ketone **15** (1.4 g, 4.9 mmol) and toluene-*p*-sulfonic acid (200 mg) in a mixture of isopropenyl acetate (15 cm^3) and acetic anhydride (15 cm^3) was heated under reflux for 2 h. The mixture was then poured into ice-water and stirred for 1.5 h, with the regular addition of solid sodium hydrogen carbonate until effervescence ceased. The resulting mixture was extracted into diethyl ether, the extract was washed (satd. aq. $NaHCO_3$, water), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (1.5 g) which was flash chromatographed on silica gel (50 g), eluting with toluene-hexane (1:1), to give the *dienyl acetate* **16** (1.25 g, 78%), m.p. 107-110°C (from methanol); $[\alpha]_D$ +108° (*c* 0.3) (Found: C, 77.9; H, 7.7%; M^+, 324. $C_{21}H_{24}O_3$ requires C, 77.7; H, 7.5%; *M*, 324); ν_{max}/cm^{-1} 1748 (C=O); δ_H (400 MHz) 1.21 (3H, s, 13β-Me), 1.94 (1H, dt, *J* 12.8 and 2 x 3.1 Hz, 12β-H), 2.21 (3H, s, 17-OAc), 2.61 (1H, dt, *J* 11.6 and 2 x 5.5 Hz, 9α-H), 2.79 (2H, m, 6-H_2), 2.94 (1H, ddd, *J* 13.3, 5.4 and 2.6 Hz, 8α-H), 3.77 (3H, s, 3-OMe), 5.98 (1H, d, *J* 3.0 Hz, 15-H), 6.08 (1H, d, *J* 3.0 Hz, 16-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.71 (1H, dd, *J* 8.4 and 2.6 Hz, 2-H) and 7.02 (1H, d, *J* 8.4 Hz, 1-H).

Cycloaddition of dienyl acetate 16 with phenyl vinyl sulfone (PVS)

A mixture of the dienyl acetate **16** (400 mg, 1.23 mmol) and PVS (1 g, 5.95 mmol) in anhydrous benzene (10 cm^3) was heated at 150°C for 140h in a sealed tube. The cooled solution was adsorbed on silica gel (50 g) and eluted with ethyl acetate-toluene (1:19) to give unidentified products (144 mg), followed by an inseparable mixture of cycloadducts **17**, **18** and **19** (476 mg, 79%). Recrystallisation from chloroform-methanol afforded 3-*methoxy*-17^{2}R-*phenylsulfonyl*-14,17α-*ethano*-8α-*estra*-1,3,5(10),15-*tetraen*-17β-*yl acetate* **17**, m.p. 286-287°C; $[\alpha]_D$ +92° (*c* 0.4) (Found: C, 70.4; H, 6.6; S, 6.4%; M^+, 492. $C_{29}H_{32}O_5S$ requires C, 70.7; H, 6.5; S, 6.5%; *M*, 492); ν_{max}/cm^{-1} 1739 (C=O) 1318, 1147 (SO_2Ph); δ_H (400 MHz) 1.03 (3H, s, 13β-Me), 2.05 (3H, s, 17β-OAc), 2.14 (1H, dd, *J* 12.2 and 9.4 Hz, 17^1_x-H), 2.57 (1H, dd, *J* 12.2 and 4.3 Hz, 17^1_n-H), 2.79 (2H, m, 6-H_2), 3.09 (2H, m, 8α-H and 9α-H), 3.78 (3H, s, 3-OMe), 4.25 (1H, dd, *J* 9.4 and 4.3 Hz, 17^2_x-H), 6.33 (1H, d, *J* 6.0 Hz, 15-H), 6.40 (1H, d, *J* 6.0 Hz, 16-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.8 Hz, 2-H), 7.04 (1H, d, *J* 8.4 Hz, 1-H), 7.50 (2H, m, *m*-H of $PhSO_2$), 7.58 (1H, m, *p*-H of $PhSO_2$) and 7.80 (2H, m, *o*-H of $PhSO_2$); δ_C (100 MHz) 16.9 (13β-Me), 21.3 (17-OC(O)*C*H_3), 22.6 (C-11), 27.2 (C-7), 28.1 (C-12), 31.1 (C-17^1), 31.3 (C-6), 34.6 (C-8), 35.4 (C-9), 55.2 (3-O*Me*), 60.3 (C-13), 61.1 (C-14), 66.3 (C-17^2), 92.4 (C-17), 112.4 (C-2), 113.2 (C-4), 128.1 (C-2'and C-6'), 129.2 (C-3' and C-5'), 130.4 (C-1), 132.5 (C-15), 132.7 (C-10), 133.3 (C-4'), 135.5 (C-16), 137.6 (C-5), 141.3 (C-1'), 157.6 (C-3) and 170.4 (17-O*C*(O)CH_3).

Base hydrolysis of cycloaddition mixture 17, 18 and 19

A solution of the mixture of cycloadducts **17**, **18** and **19** (55 mg, 0.11 mmol) in methanolic potassium hydroxide (1%; 5 cm^3) was stirred for 18h at 25°C. The mixture was poured into saturated aqueous sodium hydrogen carbonate (10 cm^3) and extracted into ethyl acetate. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude residue (39 mg) which was chromatographed on silica gel (4.5 g) with ethyl acetate-toluene (1:9) as eluent to give 3-*methoxy*-14-*phenylsulfonylethyl*-8α,14β-*estra*-1,3,5(10),15-*tetraen*-17-*one* **21** (9 mg, 17%), as an oil, $[\alpha]_D$ +14° (*c* 0.8) (Found: M^+, 450.185. $C_{27}H_{30}O_4S$ requires *M*, 450.186); ν_{max}/cm^{-1} 1708

(C=O), 1307, 1152 (SO_2Ph); δ_H (200 MHz) 1.08 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 6.20 (1H, d, *J* 5.9 Hz, 16-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.4 and 2.8 Hz, 2-H), 6.92 (1H, d, *J* 8.4 Hz, 1-H) and 7.14-7.90 (6H, m, $PhSO_2$ and 15-H) followed by an inseparable mixture of 3-methoxy-17^2*R*-phenylsulfonyl-14,17α-ethanoestra-1,3,5(10),15-tetraen-17β-ol **20** and 3-methoxy-15α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol **22** (33 mg, 66%), as an oil; *m/z* 450; ν_{max}/cm^{-1} 3599, 3412 (OH), 1307, 1148 (SO_2Ph), δ_H (400 MHz) for **22** (*ca* 70%) 0.95 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 4.00 (1H, dd, *J* 8.7 and 4.7 Hz, 15β-H), 5.96 (1H, d, *J* 5.9 Hz, 17^2-H), 6.06 (1H, d, *J* 5.9 Hz, 17^1-H), 6.57 (1H, d, *J* 2.6 Hz, 4-H), 6.66-6.74 (1H, m, 2-H), 6.98 (1H, d, *J* 8.4 Hz, 1-H), 7.48-7.88 (5H, m, 15α-SO_2*Ph*); δ_H (400 MHz) for **20** (*ca* 30%) 1.00 (1H, s, 13β-Me), 3.77 (3H, s, 3-OMe), 4.17 (1H, dd, *J* 7.8 and 5.4 Hz, 17^2_x-H), 6.06 (1H, d, *J* 5.9 Hz, 15-H), 6.31 (1H, d, *J* 5.9 Hz, 16-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.66-6.74 (1H, m, 2-H), 7.02 (1H, d, *J* 8.4 Hz, 1-H), 7.48-7.88 (5H, m, 17^2_n-SO_2*Ph*).

3-Methoxy-17^2*R*-phenylsulfonyl-14,17α-ethano-8α-estra-1,3,5(10),15-tetraen-17β-ol 20

A solution of the 17β-acetate **17** (20 mg, 0.05 mmol) in methanolic potassium hydroxide (1%, 2 cm^3) was stirred for 18h at 25°C. Work-up, as in the previous experiment, gave a crude residue (17 mg) which was chromatographed on silica gel (1.5 g) with ethyl acetate-hexane (1:1) as eluent to give the 17β-*alcohol* **20** (13 mg, 73%), as an oil, (Found: M^+, 450.185. $C_{27}H_{30}O_4S$ requires *M*, 450.186); ν_{max}/cm^{-1} 3599, 3412 (OH), 1307, 1148 (SO_2Ph); δ_H (400 MHz) 1.00 (3H, s, 13β-Me), 1.90 (1H, br. s, 17β-OH), 3.77 (3H, s, 3-OMe), 4.17 (1H, dd, *J* 7.8 and 5.4 Hz, 17^2_x-H), 6.06 (1H, d, *J* 5.9 Hz, 15-H), 6.31 (1H, d, *J* 5.9 Hz, 16-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H), 7.02 (1H, d, *J* 8.6 Hz, 1-H), 7.48-7.80 (5H, m, 17^2_n-SO_2*Ph*).

Acetylation of the mixture of alcohols 20 and 22

A solution of the two alcohols **20** and **22** (26 mg, 0.05 mmol) and 4-(dimethylamino)-pyridine (DMAP) (5 mg) in pyridine (2 cm^3) was stirred for 4h at 25°C. Saturated aqueous ammonium chloride was added and the resultant mixture was extracted into ethyl acetate. The combined organic phase was washed [aq. HCl (1 mol dm^{-3}), satd. aq. $NaHCO_3$, water, brine], dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (30 mg) which was chromatographed on silica gel (2 g) with ethyl acetate-toluene (1:19) as eluent to give a mixture of the 17β-acetates **17** and **19** (25 mg; 88%). Recrystallisation from chloroform-methanol afforded 17β-acetate **17**, m.p. 285-287°C. Evaporation of the mother liquor afforded 3-methoxy-15α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate **19** as an oil, $[\alpha]_D$ -1° (*c* 1.4) (Found: M^+, 492. $C_{29}H_{32}O_5S$ requires *M*, 492); ν_{max}/cm^{-1} 1739 (C=O), 1319, 1149 (SO_2Ph); δ_H (400 MHz) 1.00 (3H, s, 13β-Me), 2.05 (3H, s, 17β-OAc), 2.09 (1H, dd, *J* 12.3 and 9.0 Hz, 16β-H), 2.63 (1H, dd, *J* 12.3 and 4.8 Hz, 16α-H), 3.77 (3H, s, 3-OMe), 4.03 (1H, dd, *J* 9.0 and 4.8 Hz, 15β-H), 6.00 (1H, d, *J* 6.0 Hz, 17^2-H), 6.37 (1H, d, *J* 6.0 Hz, 17^1-H), 6.59 (1H, d, *J* 2.7 Hz, 4-H), 6.70 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H), 7.00 (1H, d, *J* 8.4 Hz, 1-H), 7.55 (2H, m, *m*-H of $PhSO_2$), 7.63 (1H, m, *p*-H of $PhSO_2$) and 7.88 (2H, m, *o*-H of $PhSO_2$).

Hydrogenation of the mixture of cycloadducts 17, 18 and 19

A solution of the mixture of cycloadducts **17**, **18** and **19** (460 mg, 0.9 mmol) was stirred with palladium on carbon (10%, 100 mg) in chloroform (10 cm^3) under hydrogen (50 bar) at 60°C for 5 h. The solution was filtered through Celite and the filtrate was evaporated under reduced pressure to give a solid residue (483 mg) which was adsorbed onto silica gel (50 g). Elution with ethyl acetate-toluene (1:19) gave an inseparable mixture of 3-methoxy-17^2*R*-phenylsulfonyl-14,17α-ethano-8α-estra-1,3,5(10)-trien-17β-yl acetate **23** and 3-methoxy-15α-phenylsulfonyl-14,17α-ethano-8α-estra-1,3,5(10)-trien-17β-yl acetate **24** (375 mg, 82%). Recrystallisation from chloroform-methanol afforded **24**, m.p. 312-313°C; $[\alpha]_D$ +7° (*c* 0.3) (Found: C 70.0; H, 6.9; S, 6.3%; M^+, 494. $C_{29}H_{34}O_5S$ requires C, 70.4; H, 6.9; S, 6.5%; *M*, 494); ν_{max}/cm^{-1} 1734 (C=O), 1306, 1147 (SO_2Ph); δ_H (200 MHz) 1.01 (3H, s, 13β-Me), 2.00 (3H, s, 17β-OAc), 3.79 (3H, s, 3-OMe), 3.99 (1H, ddd, *J* 11.7,

4.3 and 2.4 Hz, 15β-H or 17^2_x-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H), 7.06 (1H, d, *J* 8.5 Hz, 1-H), 7.58 (3H, m, *m*- and *p*-H of $PhSO_2$) and 7.88 (2H, m, *o*-H of $PhSO_2$) followed by 3-*methoxy*-16α-*phenylsulfonyl*-14,17α-*etheno*-8α-*estra*-1,3,5(10)-*trien*-17β-*yl acetate* **18** (82 mg, 18%), m.p. 218-220°C (from chloroform-methanol); $[\alpha]_D$ +22° (*c* 0.2) (Found: C, 70.8; H, 6.7; S, 6.3%; M^+, 492. $C_{29}H_{32}O_5S$ requires C, 70.7; H, 6.5; S, 6.5%; *M*, 492); ν_{max}/cm^{-1} 1746 (C=O), 1320, 1152 (SO_2Ph); δ_H (400 MHz) 0.91 (1H, dt, *J* 13.8 and 2 x 3.2 Hz, 12β-H), 0.95 (3H, s, 13β-Me), 1.44 (1H, qd, *J* 3 x 13.8 and 3.8 Hz, 11β-H), 1.63 (3H, s, 17β-OAc), 1.72 (1H, dd, *J* 12.6 and 4.6 Hz, 15α-H), 2.18 (1H, ddd, *J* 13.5, 4.6 and 2.4 Hz, 8α-H), 2.31 (1H, tdd, *J* 13.8, 2 x 4.2 and 0.8 Hz, 12α-H), 2.52 (1H, dd, *J* 12.6 and 9.0 Hz, 15β-H), 2.74 (2H, m, 6-H_2), 2.85 (1H, dt, *J* 12.6 and 2 x 4.2 Hz, 9α-H), 3.76 (3H, s, 3-OMe), 4.05 (1H, dd, *J* 9.0 and 4.6 Hz, 16β-H), 5.96 (1H, d, *J* 6 Hz, 17^2-H), 6.43 (1H, d, *J* 6 Hz, 17^1-H), 6.60 (1H, d, *J* 2.6 Hz, 4-H), 6.70 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H), 7.00 (1H, d, *J* 8.6 Hz, 1-H), 7.62 (3H, m, *m*- and *p*-H of $PhSO_2$) and 7.91 (2H, m, *o*-H of $PhSO_2$); δ_C (100 MHz) 16.5 (13β-Me), 20.1 (C-7), 20.9 (17-OC(O)*C*H_3), 28.2 (C-11), 28.9 (C-15), 29.2 (C-12), 30.5 (C-6), 37.8 (C-8), 38.2 (C-9), 55.2 (3-O*Me*), 54.4 (C-13), 61.2 (C-14), 67.2 (C-16), 95.1 (C-17), 112.3 (C-2), 113.2 (C-4), 128.5 (C-2' and C-6'), 129.1 (C-3' and C-5'), 129.2 ($C\text{-}17^1$), 130.4 (C-1), 133.3 (C-4'), 133.4 (C-10), 136.3 ($C\text{-}17^2$), 136.9 (C-5), 140.9 (C-1'), 157.6 (C-3) and 168.9 (17-O*C*(O)CH_3).

3-Methoxy-14,17α-ethano-8α-estra-1,3,5(10)-trien-17β-ol 25

a) A solution of 1,2-diiodoethane (1.9 g, 6.8 mmol) in THF (68 cm^3) was added slowly to samarium (1.1 g, 7.6 mmol) and the mixture was allowed to stir at 25°C until a deep blue solution was formed (*ca* 90 min). Hexamethylphosphoramide (HMPA) (5.5 cm^3) was added and the mixture was stirred for 1h at 25°C to give a dark purple solution which was cooled to -20°C. A solution of the mixture of sulfones **23** and **24** (366 mg, 0.7 mmol) in THF (35 cm^3) was added and the mixture was stirred at -20°C for 4h. Saturated aqueous ammonium chloride was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, satd. aq. $Na_2S_2O_3$, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (382 mg) which was chromatographed on silica gel (40 g) with ethyl acetate-toluene (1:19) as eluent to give starting material

(5 mg), preceded by a crude product (206 mg) which was stirred in a methanolic potassium hydroxide solution (1%, 10 cm^3) for 18h. The mixture was poured into water and extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue (181 mg) which was chromatographed on silica gel (20 g) with ethyl acetate-toluene (1:19) as eluent to give 3-*methoxy*-14,17α-*ethano*-8α-*estra*-1,3,5(10)-*trien*-17β-*ol* **25** (180 mg, 78%), m.p. 146-148°C (from methanol); $[\alpha]_D$ -34° (*c* 0.3) (Found: C, 80.5; H, 9.1%; M^+, 312. $C_{21}H_{28}O_2$ requires C, 80.7; H, 9.0%; *M*, 312); ν_{max}/cm^{-1} 3601, 3438 br. (OH); δ_H (200 MHz) 1.00 (3H, s, 13β-Me), 2.6-3.2 (3H, m, 6-H_2 and 9α-H), 3.78 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.74 (1H, dd, *J* 8.4 and 2.8 Hz, 2-H) and 7.08 (1H, d, *J* 8.4 Hz, 1-H).

b) A solution of the sulfones **23** and **24** (320 mg, 0.65 mmol) in THF (10 cm^3) was added to a solution of sodium (700 mg, 30 mmol) in a mixture of ammonia (40 cm^3, freshly distilled from sodium) and THF (5 cm^3) at -33°C. The resulting solution was stirred for 2h at -33°C. Solid ammonium chloride was added and the ammonia was allowed to evaporate. Water was added and the resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue (133 mg) which was chromatographed on silica gel (13 g) eluting with ethyl acetate-toluene (1:19) to give 3-*methoxy*-14,17α-*ethano*-8α-*estra*-1,3,5(10)-*trien*-17β-*ol* **25** (108 mg, 53%), identical in all respects (m.p., and $[\alpha]_D$) to that synthesised previously.

14,17α-ethano-8α-estra-1,3,5(10)-triene-3,17β-diol 26

A solution of boron tribromide (1.0 mol dm^{-3} in dichloromethane, 3 cm^3, 3 mmol) was added to a solution of the 3-methyl ether **25** (206 mg, 0.7 mmol) in dichloromethane (20 cm^3) at 0°C and the mixture was stirred at 0°C for 90 min. The mixture was poured into water and extracted with ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and concentrated under reduced pressure to give a residue (186 mg) which was adsorbed onto silica gel (18 g) and eluted with methanol-chloroform (1:9) to give the 3,17β-*diol* **26** (160 mg, 81%), m.p. 248-249°C (from methanol); $[\alpha]_D$ -34° (*c* 0.8

in THF) (Found: C, 80.5; H, 8.9%; M^+, 298. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.8%; *M*, 298); ν_{max}/cm^{-1} (in THF) 3442, 3320 br. (OH).

Desulfonylation of the mixture of phenyl vinyl sulfone cycloadducts 17, 18 and 19

A solution of the phenyl vinyl sulfone cycloadducts **17**, **18** and **19** (700 mg, 1.4 mmol) in THF (20 cm^3) was added to a solution of sodium (700 mg, 30 mmol) in a mixture of ammonia (40 cm^3; freshly distilled from sodium) and THF (5 cm^3) at -33°C. The resulting mixture was stirred for 2h at -33°C. Solid ammonium chloride was added, and the ammonia was allowed to evaporate. Water was added and the resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (616 mg). Chromatography on silica gel (60 g) with ethyl acetate-toluene (1:19) gave two unidentified mixtures of products (50 mg and 12 mg), followed by an inseparable mixture of products **27**, **28**, **29** and **30** (157 mg, 36%), m.p. 83-85°C (from methanol) (Found: C, 81.1; H, 8.7%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310); ν_{max}/cm^{-1} 3598 (OH); δ_H (200 MHz) 0.97 and 0.98 (3H, both s, 13β-Me), 3.77 (3H, s, 3-OMe), 5.75 (0.5H, d, *J* 5.9 Hz), 5.90 (0.5H, d, *J* 5.9Hz), 6.60 (1H, m, 4-H), 6.70 (1H, m, 2-H) and 7.01-7.05 (1H, m, 1-H).

Hydrogenation of the desulfonylation mixture 27, 28, 29 and 30

A solution of the mixture of products **27**, **28**, **29** and **30** (33 mg, 0.1 mmol) in ethyl acetate (2 cm^3) was stirred with palladium on carbon (10%, 3 mg) under hydrogen at 25°C for 3h. After filtration of the catalyst (Celite), evaporation of the filtrate gave a residue (34 mg) which was chromatographed on silica gel (5 g) with ethyl acetate-toluene (1:19) to give a mixture of the two cyclopropyl compounds **27** and **28** (17 mg, 52%). Recrystallisation from methanol afforded 3-*methoxy*-15,17^2-*cyclo*-14,17α-*ethano*-8α-*estra*-1,3,5(10)-*trien*-17β-*yl acetate* **27**, m.p. 77-80°C; $[\alpha]_D$ +2° (*c* 0.5) (Found: C, 81.1; H, 8.6%; M^+, 310. $C_{21}H_{26}O_2$ requires C, 81.3; H, 8.4%; *M*, 310); ν_{max}/cm^{-1} 3596 (OH); δ_H (400 MHz) 0.76 (1H, dt, *J* 5.8 and 2 x 1.5 Hz, 17^2-H), 0.98 (3H, s, 13β-Me), 1.44 and 1.48 (each 1H, dd, *J* 9.7 and 1.5 Hz, 16α-H and 17^1_n-H), 1.81 and 1.90 (each 1H, dt, *J* 9.7 and 2 x 1.6 Hz,

16β-H and 17^1_x-H), 3.77 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.7 Hz, 2-H), 7.06 (1H, d, *J* 8.4 Hz, 1-H). Further elution with the same solvent afforded 3-methoxy-14α,17α-ethano-8α-estra-1,3,5(10)-trien-17β-ol **25** (16 mg, 47%), m.p. 145-147°C (from methanol).

Further cycloaddition reactions of 3-methoxy-8α-estra-1,3,5(10),14,16-pentaen-17-yl acetate 16

a) With acrolein: boron trifluoride-diethyl etherate (0.1 cm^3, 0.8 mmol) was added to a cooled (0°C) solution of the dienyl acetate **16** (200 mg, 0.6 mmol) and acrolein (0.3 cm^3, 4.5 mmol) in THF (10 cm^3) and the resulting mixture was stirred at 25°C for 18h. The mixture was poured into a saturated aqueous sodium hydrogen carbonate solution, extracted into ethyl acetate (3x) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude residue (318 mg). This was chromatographed on silica gel (20 g) eluting with ethyl acetate-hexane (1:4) to give two fractions (16 and 43 mg respectively) which were mixtures of products, followed by 17β-*acetoxy*-3-*methoxy*-14,17α-*etheno*-8α-*estra*-1,3,5(10)-*triene*-16α-*carbaldehyde* **31** (127 mg, 54%), m.p. 141-143°C (from chloroform-diisopropyl ether); $[\alpha]_D$ -12° (*c* 0.2) (Found: C, 75.4; H, 7.5%; M^+, 380. $C_{24}H_{28}O_4$ requires C, 75.8; H, 7.4%; *M*, 380); ν_{max}/cm^{-1} 1734, 1710 (C=O); δ_H (400 MHz) 1.06 (3H, d, *J* 0.8 Hz, 13β-Me), 1.12 (1H, dt, *J* 13.2 and 2 x 3.4 Hz, 12β-H), 1.33 (1H, dd, *J* 12.4 and 4.1 Hz, 15α-H), 2.11 (3H, s, 17β-OAc), 2.45 (1H, dd, *J* 12.4 and 9.1 Hz, 15β-H), 2.7-2.90 (3H, m, 6-H_2 and 9α-H), 3.15 (1H, ddd, *J* 9.1, 4.5 and 4.1 Hz, 16β-H), 3.77 (3H, s, 3-OMe), 6.02 (1H, d, *J* 6 Hz, 17^2-H), 6.36 (1H, d, *J* 6 Hz, 17^1-H), 6.61 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.6 Hz, 2-H), 7.02 (1H, d, *J* 8.4 Hz, 1-H) and 9.47 (1H, d, *J* 4.5 Hz, 16-C*H*O); δ_C (100 MHz) 16.4 (13β-Me), 20.1 (C-7), 21.3 (17-OC(O)*C*H_3), 28.1 (C-11), 28.3 (C-15), 30.6 (C-6), 30.9 (C-12), 38.0 (C-8), 38.6 (C-9), 54.4 (C-14), 55.2 (C-16), 55.2 (3-O*Me*), 59.3 (C-13), 95.5 (C-17), 112.3 (C-2), 113.2 (C-4), 129.8 ($C\text{-}17^1$), 130.4 (C-1), 133.5 (C-10), 137.1 (C-5), 140.2 ($C\text{-}17^2$), 157.6 (C-3), 171.2(17-O*C*(O)CH_3) and 201.9 (16-*C*HO).

b) With methyl propiolate: a solution of the dienyl acetate **16** (430 mg, 1.3 mmol) and methyl propiolate (0.6 cm^3, 6.7 mmol) in benzene (6 cm^3) was heated in a sealed tube at 100°C for 72h. The cooled solution was adsorbed onto silica gel (40 g) and eluted with ethyl acetate-toluene (1:19) to give an unidentified mixture of products (54 mg), followed by *methyl* 17β-*acetoxy*-3-*methoxy*-14,17α-*etheno*-8α-*estra*-1,3,5(10),15-*tetraene* 16-*carboxylate* **33** (361 mg, 66%), m.p. 177-178°C (from benzene-hexane); $[\alpha]_D$ -50° (*c* 0.4) (Found: C, 73.7; H, 7.0%; M^+, 408. $C_{25}H_{28}O_5$ requires C, 73.5; H, 6.9%; *M*, 408); ν_{max}/cm^{-1} 1742, 1711 (C=O); δ_H (400 MHz) 1.25 (3H, d, *J* 0.8 Hz, 13β-Me), 1.36 (1H, dt, *J* 12.7 and 2 x 3.2 Hz, 12β-H), 1.54 (1H, qd, *J* 3x13.8 and 3.8 Hz, 11β-H), 1.66 (1H, dq, *J* 13.8 and 3 x 3.8 Hz, 11α-H), 1.74-1.88 (2H, m, 7-H_2), 2.18 (3H, s, 17β-OAc), 2.40-2.50 (2H, m, 8α-H and 12α-H), 2.74-2.90 (3H, m, 6-H_2 and 9α-H), 3.72 (3H, s, 16-CO_2*Me*), 3.77 (3H, s, 3-OMe), 6.40 (1H, d, *J* 5.1 Hz, 17^2-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.4 and 2.8 Hz, 2-H), 7.04 (1H, d, *J* 8.4 Hz, 1-H), 7.05 (1H, d, *J* 5.1 Hz, 17^1-H) and 7.50 (1H, s, 15-H); δ_C (100 MHz) 18.6 (13β-Me), 21.4 (17-OC(O)*C*H_3), 21.6 (C-7), 27.4 (C-11), 30.4 (C-12), 30.8 (C-6), 36.1 (C-8), 37.4 (C-9), 51.3 (16-CO_2*Me*), 55.2 (3-O*Me*), 64.8 (C-14), 87.4 (C-13), 98.7 (C-17), 112.3 (C-2), 113.3 (C-4), 130.4 (C-1), 133.2 (C-10), 136.9 (C-5), 140.0 ($C\text{-}17^1$), 143.5 ($C\text{-}17^2$), 146.8 (C-16), 152.8 (C-15), 157.6 (C-3), 164.7 (16-*C*O_2Me) and 170.7 (17-O*C*(O)CH_3).

c) With 2-acetoxyacrylonitrile: a solution of the dienyl acetate **16** (200 mg, 0.6 mmol), hydroquinone (50 mg) and 2-acetoxyacrylonitrile (0.1 cm^3, 0.9 mmol) in benzene (3 cm^3) was heated in a sealed tube at 150°C for 288h. Further aliquots of dienophile (0.1 cm^3) were added after 40, 96, 140, 188 and 236h. The cooled mixture was adsorbed onto silica gel (20 g) and eluted with ethyl acetate-toluene (1:19) to give starting material (27 mg, 13%) followed by 16α,17β-*diacetoxy*-3-*methoxy*-14,17α-*etheno*-8α-*estra*-1,3,5(10)-*triene*-16β-*carbonitrile* **37** (174 mg, 65%), m.p. 177-179°C (from dichloromethane-methanol); $[\alpha]_D$ +92° (*c* 0.4) (Found: C, 71.8; H, 6.8; N, 3.1%; M^+, 435. $C_{26}H_{29}NO_5$ requires C, 71.7, H 6.7; N, 3.2%; *M*, 435); ν_{max}/cm^{-1} 2238 (CN), 1745 (C=O); δ_H (400 MHz) 1.12 (1H, dt, *J* 13.4 and 2 x 3.2 Hz, 12β-H), 1.29 (3H, d, *J* 0.8 Hz, 13β-Me), 1.54 (1H, qd, *J* 3 x 13.6 and 3.9 Hz, 11β-H), 1.62 (1H, d, *J* 14 Hz, 15α-H), 2.07 (3H, s, 16α-OC(O)C*H*$_3$), 2.11 (1H, ddd, *J* 13.3, 4.9 and 13.3 Hz, 8α-H), 2.20 (3H, s, 17β-OAc), 2.36 (1H, tdd, *J* 2 x 13.6, 4.8 and 0.8 Hz, 12α-H), 2.7 (1H, m, 6-H), 2.84 (2H, m, 6-H_2 and 9α-H), 3.12 (1H, d, *J* 14 Hz,

15β-H), 3.76 (3H, s, 3-OMe), 6.02 (1H, d, *J* 6 Hz, 17^2-H), 6.36 (1H, d, *J* 6 Hz, 17^1-H), 6.60 (1H, d, *J* 2.6 Hz, 4-H), 6.71 (1H, dd, *J* 8.4 and 2.6 Hz, 2-H) and 7.00 (1H, d, *J* 8.4 Hz, 1-H); δ_C (100 MHz) 17.7 (13β-Me), 19.8 (C-7), 20.9 (16-OC(O)*C*H_3), 21.3 (17-OC(O)*C*H_3), 27.7 (C-11), 30.2 (C-12), 30.4 (C-6), 37.5 (C-8), 37.8 (C-9), 42.3 (C-15), 54.8 (C-14), 55.1 (3-O*Me*), 59.7 (C-13), 79.0 (C-16), 97.7 (C-17), 112.3 (C-2), 113.1 (C-4), 117.1 (16-*C*N), 130.2 (C-1), 130.6 ($C\text{-}17^1$), 132.9 (C-10), 136.8 (C-5), 139.5 ($C\text{-}17^2$), 157.6 (C-3), 169.0 and 169.2 [16-O*C*(O)CH_3 and 17-O*C*(O)CH_3]. Further elution with the same solvent gave an unidentified mixture of products (10 mg).

Sodium borohydride reduction of methyl propiolate adduct 33

A solution of the methyl propiolate cycloadduct **33** (277 mg, 0.7 mmol) in a mixture of THF (21 cm^3) and methanol (3 cm^3) was stirred at 25°C while sodium borohydride (100 mg, 2.6 mmol) was added portionwise. The mixture was stirred for 15 min at 25°C, poured into water (25 cm^3) and extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give a crude residue (281 mg) which was chromatographed on silica gel (30 g) with ethyl acetate-hexane (1:4) as eluent to give *methyl* 17β-*acetoxy*-3-*methoxy*-14,17α-*etheno*-8α-*estra*-1,3,5(10)-*triene* 16β-*carboxylate* **35** (130 mg, 47%), m.p. 128-130°C (from methanol); $[\alpha]_D$ +34° (*c* 1.6) (Found: C, 73.2; H, 7.5%; M^+, 410. $C_{25}H_{30}O_5$ requires C, 73.1; H, 7.4%; *M*, 410); ν_{max}/cm^{-1} 1732 (C=O); δ_H (400 MHz) 0.97 (3H, d, *J* 0.4 Hz, 13β-Me), 1.18 (1H, dt, *J* 13 and 2 x 3.2 Hz, 12β-H), 2.15 (3H, s, 17β-OAc), 2.65 (1H, dd, *J* 12.4 and 4.6 Hz, 15β-H), 3.25 (1H, dd, *J* 9.6 and 4.6 Hz, 16α-H), 3.69 (3H, s, 16β-CO_2*Me*), 3.77 (3H, s, 3-OMe), 5.90 (1H, d, *J* 5.7 Hz, 17^2-H), 6.40 (1H, d, *J* 5.7 Hz, 17^1-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.6 Hz, 2-H) and 7.02 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 16.1 (13β-Me), 20.2 (17-OC(O)*C*H_3), 21.5 (C-7), 28.3 (C-11), 28.7 (C-15), 30.7 (C-12), 31.6 (C-6), 38.0 (C-8), 38.2 (C-9), 44.9 (C-16), 51.7 (16β-CO_2*Me*), 53.2 (C-14), 55.2 (3-O*Me*), 57.4 (C-13), 94.7 (C-17), 112.2 (C-2), 113.2 (C-4), 130.4 (C-1), 133.7 (C-10), 134.3 ($C\text{-}17^1$), 137.2 (C-5), 141.0 ($C\text{-}17^2$), 157.5 (C-3), 171.6 (17-O*C*(O)CH_3) and 173.0 (16β-*C*O_2Me), followed by mixed fractions (43 mg, 15%), and *methyl* 17β-*acetoxy*-3-*methoxy*-14,17α-*etheno*-8α-*estra*-1,3,5(10)-*triene* 16α-*carboxylate* **34** (61 mg, 22%) as a glass, $[\alpha]_D$ +17° (*c* 5.0) (Found: C, 72.5; H, 7.5%;

M^+, 410. $C_{25}H_{30}O_5$ requires C, 73.1; H, 7.4%; *M*, 410); ν_{max}/cm^{-1} 1740 (C=O); δ_H (200 MHz) 1.03 (3H, s, 13β-Me), 2.10 (3H, s, 17β-OAc), 2.40 (1H, dd, *J* 12 and 9 Hz, 15β-H), 3.25 (1H, dd, *J* 9 and 4.2 Hz, 16β-H), 3.64 (3H, s, 16α-CO_2*Me*), 3.76 (3H, s, 3-OMe), 5.90 (1H, d, *J* 6.1 Hz, 17^2-H), 6.33 (1H, d, *J* 6.1 Hz, 17^1-H), 6.61 (1H, d, *J* 2.5 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H) and 7.01 (1H, d, *J* 8.5 Hz, 1-H), δ_C (50 MHz) 16.6 (13β-Me), 20.1 (17-OC(O)*C*H_3), 21.4 (C-7), 28.4 (C-11), 29.0 (C-15), 30.6 (C-12), 31.2 (C-6), 38.0 (C-8), 38.4 (C-9), 46.6 (C-16), 51.6 (16α-CO_2*Me*), 54.1 (C-14), 55.1 (3-O*Me*), 59.6 (C-13), 95.9 (C-17), 112.2 (C-2), 113.1 (C-4), 130.2 ($C\text{-}17^1$), 130.3 (C-1), 133.7 (C-10), 137.0 (C-5), 137.8 ($C\text{-}17^2$), 157.5 (C-3), 170.0 (17-O*C*(O)CH_3) and 173.9 (16α-*C*O_2Me).

14-Allyl-3-methoxy-8α,14β-estra-1,3,5(10),15-tetraen-17-one 32

a) A solution of the 16β-methyl carboxylate **35** (130 mg, 0.3 mmol) in THF (20 cm^3) was stirred with LAH (100 mg, 2.6 mmol) for 18h at 25°C. Ethyl acetate (2 cm^3) was added and the reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution. The resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (104 mg) which was chromatographed on silica gel (8 g) with ethyl acetate-toluene (2:3) to give a solid residue (87 mg). This was stirred with toluene-*p*-sulfonyl chloride (100 mg, 0.5 mmol) in pyridine (2 cm^3) for 2h. Saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted with ethyl acetate. The combined organic extracts were washed [satd. aq. $NaHCO_3$, aq. HCl (1 mol dm^{-3}), water, brine], dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (90 mg). The was refluxed with methanolic potassium hydroxide (1%, 25 cm^3) for 90 min. Saturated aqueous ammonium chloride was added to the cooled solution and it was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (70 mg) which was filtered through silica gel (10 g) with ethyl acetate-toluene (1:19) as eluent to give the 14β-*allyl* Δ^{15} 17-*ketone* **32** (37 mg, 46% from **35**), m.p. 118-121°C (from diisopropyl ether); $[\alpha]_D$ +68° (*c* 0.6) (Found: C, 82.0; H, 8.3%; M^+, 322. $C_{22}H_{26}O_2$ requires C, 81.9; H, 8.1%; *M*, 322); ν_{max}/cm^{-1} 1703 (C=O); δ_H (400 MHz) 1.18 (3H, s, 13β-Me), 2.18 (1H, ddd,

J 13.0, 4.5 and 2.6 Hz, 8α-H), 2.61 (1H, m, 14^1-H), 3.77 (3H, s, 3-OMe), 5.08-5.14 (2H, m, 14^3-H_2), 5.7-5.8 (1H, m, 14^2-H), 6.15 (1H, d, *J* 5.8 Hz, 16-H), 6.60 (1H, d, *J* 2.6 Hz, 4-H), 6.69 (1H, dd, *J* 8.3 and 2.6 Hz, 2-H), 6.94 (1H, d, *J* 8.3 Hz, 1-H) and 7.50 (1H, d, *J* 5.8 Hz, 15-H); δ_C (50 MHz) 17.1 (13β-Me), 20.0 (C-7), 28.4 (C-11), 30.3 (C-12), 35.4 (C-6), 37.5 (C-9), 39.3 (C-14^1), 44.6 (C-8), 51.3 (C-14), 53.6 (C-13), 55.2 (3-O*Me*), 112.3 (C-2), 113.0 (C-4), 118.7 (C-14^3), 129.8 (C-1), 130.0 (C-14^2), 133.8 (C-10), 136.5 (C-5), 157.6 (C-3), 170.7 (C-15) and 213.9 (C-17).

b) A solution of the acrolein cycloadduct **31** (55 mg, 0.1 mmol) in THF (5 cm^3) was stirred while LAH (50 mg, 1 mmol) was added and the mixture was stirred for 10 min, ethyl acetate (2 cm^3) was added and the mixture was poured into saturated aqueous sodium hydrogen carbonate (20 cm^3). The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (60 mg) which stirred with toluene-*p*-sulfonyl chloride (100 mg, 0.5 mmol) in pyridine (2 cm^3) at 25°C for 15 min and then stored at 7°C for 48h. Saturated aqueous sodium hydrogen carbonate was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed [aq. HCl (1 mol dm^{-3}), water, brine], dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue (60 mg) which was refluxed in methanolic potassium hydroxide (1%, 10 cm^3) for 30 min. Saturated aqueous ammonium chloride was added to the cooled solution and work-up [as in (**a**)] gave a solid residue (36 mg) which was chromatographed on silica gel (5 g) with ethyl acetate-toluene (1:19) as eluent to give the 14β-allyl-Δ^{15} 17-ketone **32** [26 mg, 58% from **31**] which was identical in all respects (m.p., mixed m.p., $[\alpha]_D$, and ^{1}H NMR) with that synthesised in the previous experiment.

17β-Hydroxy-3-methoxy-14,17α-etheno-8α-estra-1,3,5(10)-trien-16-one 38

Aqueous potassium hydroxide (2 mol dm^{-3}, 5 cm^3) was added to a solution of the 2-acetoxyacrylonitrile cycloadduct **37** (70 mg, 0.2 mmol) in a mixture of dimethylsulfoxide (DMSO) (2 cm^3) and THF (2 cm^3) and the resulting mixture was stirred for 5h at 25°C. Saturated aqueous ammonium chloride was added and the mixture was extracted into ethyl acetate. The extract was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (66 mg) which was chromatographed on silica gel (10 g)

with ethyl acetate-toluene (1:9) as eluent to give the 17β-*hydroxy* 16-*ketone* **38** (32 mg, 62%), m.p. 170-172°C (from chloroform-methanol); $[\alpha]_D$ +387° (*c* 0.2) (Found: C, 77.7; H, 7.7%; M^+, 324. $C_{21}H_{24}O_3$ requires C, 77.7; H, 7.5%; *M*, 324); ν_{max}/cm^{-1} 3523, 3402 (OH), 1746 (C=O); δ_H (200 MHz) 1.00 (3H, s, 13β-Me), 1.98 (1H, d, *J* 16.8 Hz, 15β-H), 2.44 (1H, d, *J* 16.8 Hz, 15α-H), 3.78 (3H, s, 3-OMe), 5.83 (1H, d, *J* 5.9 Hz, 17^2-H), 6.22 (1H, d, *J* 5.9 Hz, 17^1-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.74 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H) and 7.06 (1H, d, *J* 8.5 Hz, 1-H).

3-Methoxy-14,17α-etheno-8α-estra-1,3,5(10)-triene-16β,17β-diol 39

a) Sodium borohydride (60 mg, 1.6 mmol) was added to a solution of the 2-acetoxyacrylonitrile cycloadduct **37** (60 mg, 0.1 mmol) in methanol (5 cm^3) and the mixture was stirred at 25°C for 20h. Water was added, and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (50 mg) which was adsorbed onto silica gel (5 g) and eluted with ethyl acetate-toluene (1:4) to give an unidentified impurity (3 mg) followed by the 16β,17β-*diol* **39** (26 mg, 57%), m.p. 135-136 °C (from methanol); $[\alpha]_D$ +29° (*c* 0.3) (Found: C, 77.1; H, 8.2%; M^+, 326. $C_{21}H_{26}O_3$ requires C, 77.3; H, 8.0%; *M*, 326); ν_{max}/cm^{-1} 3690, 3611, 3566 (OH); δ_H (200 MHz) 1.17 (3H, s, 13β-Me), 2.22 and 2.62 (each 1H, br. s, 16β- and 17β-OH), 3.77 (3H, s, 3-OMe), 3.90 (1H, dd, *J* 7.7 and 2.4 Hz, 16α-H), 5.76 (1H, d, *J* 5.9 Hz, 17^2-H), 5.89 (1H, d, *J* 5.9 Hz, 17^1-H), 6.62 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.3 and 2.6 Hz, 2-H) and 7.04 (1H, d, *J* 8.3 Hz, 1-H).

b) Lithium aluminium hydride (60 mg, 1.6 mmol) was added to a solution of the 17β-hydroxy 16-ketone **38** (30 mg, 0.1 mmol) in THF (5 cm^3) and the mixture was stirred for 30 min. Work-up, as in (**a**) followed by recrystallisation from methanol afforded the 16β,17β-diol **39** (25 mg, 83%) m.p. 134-135°C.

14-Formylmethyl-3-methoxy-8α,14β-estra-1,3,5(10),15-tetraen-17-one 40

A solution of the 16β,17β-diol **39** (10 mg, 0.03 mmol) in ethanol (2 cm^3) was stirred at 25°C while aqueous sodium periodate (6%, 2 cm^3) was added and the resulting mixture was stirred for 10 min. Ethylene glycol and water were added, and the product was isolated by extraction with chloroform. Flash chromatography on silica gel (1 g) with ethyl acetate-toluene (1:9) as eluent gave the product **40** (6 mg, 62%), as an oil (Found: M^+, 324. $C_{21}H_{24}O_3$ requires *M*, 324); ν_{max}/cm^{-1} 1710 (C=O); δ_H (400 MHz) 1.14 (3H, s, 13β-Me), 2.15 (1H, dd, *J* 16.6 and 1.1 Hz, 14^1-H), 3.17 (1H, dd, *J* 16.6 and 2.3 Hz, 14^1-H), 3.75 (3H, s, 3-OMe), 6.17 (1H, d, *J* 6.0 Hz, 17^1-H), 6.58 (1H, d, *J* 2.6 Hz, 4-H), 6.68 (1H, dd, *J* 8.4 and 2.6 Hz, 2-H), 6.92 (1H, d, *J* 8.3 Hz, 1-H), 7.80 (1H, d, *J* 6.0 Hz, 17^2-H) and 9.80 (1H, dd, *J* 2.3 and 1.1 Hz, 14^1-C*H*O). The lability of the product precluded further characterisation.

17,17-Ethylenedioxy-3-methoxy-9β-estra-1,3,5(10)-trien-11α-yl 11-methyl xanthate 44

Sodium borohydride (500 mg, 12.5 mmol) was added to a solution of 17,17-ethylenedioxy-3-methoxy-9β-estra-1,3,5(10)-trien-11-one **42** [100] (465 mg, 1.4 mmol) in a mixture of THF (10 cm^3) and water (1 cm^3) and the mixture was stirred for 2h. Water was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give crude 11α-alcohol **43** (438 mg), δ_H (200 MHz) 1.02 (3H, s, 13β-Me), 3.50 (1H, br. m, 9β-H), 3.77-3.85 (4H, m, 17,17-OCH_2CH_2O), 3.77 (3H, s, 3-OMe), 4,45 (1H, dt, *J* 7.5 and 2 x 4.6 Hz, 11β-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.8 and 2.7 Hz, 2-H) and 7.77 (1H, d, *J* 8.8 Hz, 1-H). The 11α-alcohol **43** (430 mg, 1.3 mmol), sodium hydride (0.5 g of a 60% suspension in mineral oil, 12.5 mmol) and imidazole (10 mg) were refluxed in THF (20ml) for 90 min. Carbon disulfide (0.2 cm^3, 3 mmol) was added and the mixture was refluxed for 30 min, then methyl iodide (0.2 cm^3, 3 mmol) was added. The resulting mixture was refluxed for 30 min. Acetic acid (2 cm^3) was added to the cooled solution and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (826 mg) which was chromatographed on silica gel (50 g) with ethyl acetate-hexane (1:9) as eluent to give the

11α-xanthate **44** (402 mg, 74%), as an oil, $[\alpha]_D$ +50° (*c* 0.3) (Found: M^+, 434. $C_{23}H_{30}O_4S_2$ requires *M*, 434); ν_{max}/cm^{-1} 1235, 1120, 1052 (C=S); δ_H (200 MHz) 1.09 (3H, s, 13β-Me), 2.56 (3H, s, 11α-OCS_2*Me*), 3.50 (1H, t, *J* 2 x 4.3 Hz, 9β-H), 3.75-3.9 (4H, m, 17,17-OCH_2CH_2O), 3.78 (3H, s, 3-OMe), 6.30 (1H, dt, *J* 10.9 and 2 x 4.3 Hz, 11β-H), 6.63 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.8 and 2.7 Hz, 2-H) and 7.61 (1H, d, *J* 8.8 Hz, 1-H).

3-Methoxy-17-oxo-9β-estra-1,3,5(10)-trien-11α-yl 11-methyl xanthate 45

A solution of the 17-ketal **44** (87 mg, 0.2 mmol) and toluene-*p*-sulfonic acid (30 mg) in a mixture of acetone and water (7:1; 16 cm^3) was stirred for 22h at 25°C. The residue after evaporation of the solvent under reduced pressure was dissolved in ethyl acetate. The resulting solution was washed (satd. aq. $NaHCO_3$, water), dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue which was chromatographed on silica gel (5 g) with ethyl acetate-toluene (1:19) as eluent to give the 17-*ketone* **45** (66 mg, 85%), m.p. 152-154°C (from acetone-hexane); $[\alpha]_D$ +161° (*c* 0.4) (Found: C, 64.9; H, 6.9; S, 16.4%; M^+, 390. $C_{21}H_{26}O_3S_2$ requires C, 64.6; H, 6.7; S, 16.4%; *M*, 390); ν_{max}/cm^{-1} 1734 (C=O), 1239, 1150, 1055 (C=S); δ_H (200 MHz) 1.11 (3H, s, 13β-Me), 2.53 (3H, s, 11α-OCS_2*Me*), 3.50 (1H, t, *J* 2 x 4.7 Hz, 9β-H), 3.77 (3H, s, 3-OMe), 6.31 (1H, dt, *J* 8.3 and 2 x 4.6 Hz, 11β-H), 6.64 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H) and 7.51 (1H, d, *J* 8.5 Hz, 1-H).

3-Methoxy-9β-estra-1,3,5(10)-trien-17-one 46

a) A solution of the 17,17-ethylenedioxy-11α-xanthate **45** (100 mg, 0.2 mmol), tributylstannane (1 g, 3.4 mmol) and α,α'-azobis(isobutyronitrile) (AIBN) (30 mg) in toluene (5ml) was refluxed for 3h. The cooled mixture was adsorbed onto silica gel (20 g) and eluted with toluene (to remove the tin residues) followed by ethyl acetate-toluene (1:19) to give an oily residue (36 mg, 0.1 mmol) which was dissolved in a mixture of acetone and water (7:1; 10 cm^3) and stirred with toluene-*p*-sulfonic acid (10 mg) for 18h. The acetone was removed under reduced pressure and the resulting solution was extracted with ethyl acetate. The combined organic phase was washed (satd. aq. $NaHCO_3$, water,

brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (25 mg) which was filtered through silica gel (0.5 g) with ethyl acetate-toluene (1:19) to give 3-methoxy-9β-estra-1,3,5(10)-trien-17-one **46** (18 mg, 28%) as an oil, $[\alpha]_D$ +40° (*c* 0.2) (lit., [115] $[\alpha]_D$ +43°) (Found: M^+, 284. $C_{19}H_{24}O_2$ requires *M*, 284); ν_{max}/cm^{-1} 1728 (C=O); δ_H (400 MHz) 0.97 (3H, s, 13β-Me), 1.24 (1H, td, *J* 2 x 12.8 and 3.8 Hz, 12α-H), 2.20 (1H, m, 8β-H), 2.70 (1H, dt, *J* 16.8 and 2 x 4.6 Hz, 6β-H), 2.80 (1H, td, *J* 2 x 16.8 and 8.8 Hz, 6α-H), 3.01 (1H, br. s, $W_{½}$ 10 Hz, 9β-H), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.22 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 13.4 (13β-Me), 21.8 (C-15), 24.2 (C-11), 24.8 (C-7), 26.0 (C-6), 27.4 (C-12), 33.8 (C-8), 35.4 (C-16), 37.3 (C-9), 42.3 (C-14), 47.9 (C-13), 55.2 (3-O*Me*), 112.0 (C-2), 113.9 (C-4), 127.4 (C-1), 129.6 (C-10), 138.4 (C-5), 157.5 (C-3) and 220.8 (C-17).

b) A solution of the 17-oxo 11α-xanthate **45** (90 mg, 0.2 mmol) and AIBN (30 mg) in toluene (10 cm^3) was added to tributylstannane (1 g) and the mixture was refluxed for 48h. Further tributylstannane (1 g) and AIBN (40 mg) were added after 24h. The cooled mixture was adsorbed onto silica gel (20 g) and eluted with toluene (to remove the tin residues) followed by ethyl acetate-toluene (2:3) to give an oily residue (342 mg) which was dissolved in dichloromethane (5 cm^3). Dess-Martin periodinane [72] (200 mg, 0.5 mmol) was added and the mixture was stirred for 3h, poured into a solution of sodium thiosulfate (500 mg) in saturated aqueous sodium hydrogen carbonate (20 cm^3) and extracted into diethyl ether. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (350 mg) which was chromatographed on silica gel (30 g) with ethyl acetate-toluene (1:9) to give 3-methoxy-9β-estra-1,3,5(10)-trien-17-one **46** (9 mg, 14%), identical with that described in the previous experiment.

17-Oxoestra-1,3,5(10)-trien-3-yl acetate 47

A solution of estrone **41** (1.63 g, 6 mmol) and toluene-*p*-sulfonic acid (100 mg) in acetic anhydride (20 cm^3) was stirred at 25°C under nitrogen for 18h. Ice and solid sodium hydrogen carbonate were added and the solution was extracted into ethyl acetate (3x). After removal of the solvent, crystallisation of the residue from ethanol afforded the 3-acetate **47** (1.69 g, 90%), m.p. 123-126°C (lit., [187] 125-127°C).

17-Oxoestra-1,3,5(10),9(11)-tetraen-3-yl acetate 49

a) To a solution of estrone 3-acetate **47** (174 mg, 0.6 mmol) in dichloromethane was added tetrabutylammonium hydrogen sulfate (100 mg), acetone (10 cm^3) and phosphate buffer [188] (pH 7.5, 25 cm^3). The mixture was cooled in an ice bath and the pH adjusted to 7.5 (5 mol dm^{-3} aq. potassium hydroxide). A solution of oxone® (9 g) and disodium ethylenediaminetetraacetate (200 mg) in distilled water (60 cm^3) was added dropwise over 7h, while maintaining the temperature and pH at 0-5°C and 7.5 respectively. The mixture was stirred for a further 17h at 4°C. The dichloromethane solution was separated, dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (218 mg) which was adsorbed onto silica gel (20 g) and flash chromatographed with ethyl acetate-toluene (1:9) to give starting material **47** (90 mg, 52%) followed by 9α-hydroxy-17-oxoestra-1,3,5(10)-trien-3-yl acetate **48** (55 mg, 30%), m.p. 152-155°C (from ethanol) (lit., [101, 116] 165-166°C, 162-164°C); ν_{max}/cm^{-1} 3682, 3598 (OH), 1733 cm^{-1} (C=O); δ_H (200 MHz) 0.88 (3H, s, 13β-Me), 2.28 (3H, s, 3-OAc), 6.86 (1H, d, *J* 2.5 Hz, 4-H), 6.92 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H) and 7.54 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 12.9 (13β-Me), 20.0 (3-OC(O)*C*H_3), 21.1 (C-7), 21.4 (C-15), 27.7 (C-12), 29.4 (C-6), 32.2 (C-11), 35.9 (C-16), 41.1 (C-8), 43.1 (C-14), 47.6 (C-13), 70.0 (C-9), 119.6 (C-2), 122.3 (C-4), 126.5 (C-1), 138.4 (C-5), 139.2 (C-10), 150.0 (C-3), 169.6 (3-O*C*(O)CH_3) and 220.4 (C-17).

Toluene-*p*-sulfonic acid (100 mg) was added to a stirred solution of the 9α-alcohol **48** (81 mg, 0.3 mmol) in dry benzene (10 cm^3) and the mixture stirred at 25°C for 7h. Solid sodium hydrogen carbonate and water were added and the mixture was extracted into toluene (3x). The combined organic phase was washed (water), dried ($MgSO_4$) and

evaporated under reduced pressure to give a residue (73 mg) which was adsorbed onto silica gel (7 g) and eluted with ethyl acetate-toluene (1:9) to give 17-oxoestra-1,3,5(10),9(11)-tetraen-3-yl acetate **49** (50 mg, 65%), m.p. 122-125°C (from methanol) (lit., [101] 124-127°C); *m/z* 310; δ_H (200 MHz) 0.92 (3H, s, 13β-Me), 2.27 (3H, s, 3-OAc), 6.22 (1H, m, 11-H), 6.80-6.90 (2H, m, 2- and 4-H) and 7.58 (1H, d, *J* 8.5 Hz, 1-H) followed by unidentified coloured material (20 mg).

b) To a solution of estrone 3-acetate **47** (100 mg, 0.3 mmol) in acetone (2 cm^3) was added a freshly prepared solution of dimethyldioxirane in acetone [117] (*ca.* 0.1 mol dm^{-3}, 8.5 cm^3, 0.85 mmol). The mixture was allowed to stir for 48h at 25°C. The acetone was removed under reduced pressure to give a residue (100 mg) which was dissolved in benzene (10 cm^3) and stirred with toluene-*p*-sulfonic acid (100 mg) at 25°C for 18h. Solid sodium hydrogen carbonate and water were added and the mixture was extracted into toluene (3x). The combined organic phase was washed with water (1x), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (100 mg) which was absorbed onto silica gel (10 g) and eluted with ethyl acetate-toluene (1:9) to give the $\Delta^{9(11)}$ 3-acetate **49** (36 mg, 35% from **47**).

Estra-1,3,5(10),9(11)-tetraen-3,17β-diyl diacetate 50

A solution of estrone **41** (5 g, 18.5 mmol) in dry methanol (800 cm^3) was stirred at 25°C while a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (4.3 g, 18.9 mmol) in methanol (30 cm^3) was added over 2 min. The resulting dark purple solution was stirred for 100 min at 25°C. The methanol was evaporated under reduced pressure and the resulting brown solid was triturated with chloroform (500 cm^3) and allowed to stand for 18h. Activated charcoal was then added and the mixture was stirred for 5 min and then filtered through Celite to give a pale yellow solution. Removal of the chloroform gave a yellow-brown crystalline residue (7.4 g) which was dissolved in a mixture of THF (120 cm^3) and methanol (20 cm^3). Sodium borohydride (1.5 g, 39.5 mmol) was added and the mixture was stirred for 30 min at 25°C. Water was added and the resulting mixture was extracted into chloroform. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (6.1 g) which was

dissolved in a mixture of THF (15 cm^3) and acetic anhydride (5 cm^3). Toluene-*p*-sulfonic acid (200 mg) was added and the mixture was stirred for 18 h at 25°C. Water and solid sodium hydrogen carbonate were added until effervescence ceased. The resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (7.2 g) which was recrystallised from methanol to give impure estra-1,3,5(10),9(11)-tetraen-3,17β-diyl diacetate **50** (3.63 g, 55%), m.p. 140-142°C (lit., [103] 134-135°C, [121] 149°C); δ_H (200 MHz) (*ca.* 90%) 0.82 (3H, s, 13β-Me), 2.06 (3H, s, 17β-OAc), 2.26 (3H, s, 3-OAc), 2.85 (2H, m, 6-H_2), 4.75 (1H, dd, *J* 8.9 and 7.2 Hz, 17α-H), 6.20 (1H, dt, *J* 5.5 and 2 x 2.3 Hz, 11-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.66 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.56 (1H, d, *J* 8.6 Hz, 1-H); δ_H (200 MHz) (*ca.* 10%) 0.80 (3H, s, 13β-Me), 2.04 (3H, s, 17β-OAc), 2.27 (3H, s, 3-OAc), 4.75 (1H, dd, *J* 8.9 and 7.2 Hz, 17α-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.66 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.25 (1H, d, *J* 8.6 Hz, 1-H). The mother liquor material was flash chromatographed on silica gel (165 g) with toluene (for 3 column volumes) followed by ethyl acetate-toluene (1:9) to give further impure $\Delta^{9(11)}$ 3,17β diacetate **50** (2.27 g, 35%).

11-Oxo-9β-estra-1,3,5(10)-triene-3,17β-diyl diacetate 51

A solution of dimethyldioxirane in acetone (*ca.* 0.1 mol dm^{-3}, 75 cm^3, 7.5 mmol) was added to the $\Delta^{9(11)}$ 3,17β-diacetate **50** (2.42 g, 6.8 mmol) and the mixture was stirred for 2h at 25°C. The acetone was evaporated under reduced pressure and the residue was dissolved in benzene (60 cm^3). Lithium perchlorate (200 mg) was added and the mixture was refluxed for 1h. The cooled solution was washed with water and evaporated under reduced pressure to give a residue (2.35 g) which was flash chromatographed on silica gel (165 g) with ethyl acetate-hexane (1:4) as eluent to give estra-1,3,5(10)-triene-3,17β-diyl diacetate (312 mg, 13%), m.p. 95-97°C (from methanol) (lit., [189] 97-98°C); *m/z* 356, followed by the 11-*ketone* **51** (1.27 g, 50%), as a foam, $[\alpha]_D$ +133° (*c* 0.3) (Found: C, 70.8; H, 7.2%; M^+, 370. $C_{22}H_{26}O_5$ requires C, 71.3; H, 7.1%; *M*, 370); ν_{max}/cm^{-1} 1726 (C=O); δ_H (400 MHz) 0.84 (3H, s, 13β-Me), 2.00 (3H, s, 17β-OAc), 2.27 (3H, s, 3-OAc), 2.68-2.92 (2H, m, 6-H_2), 3.62 (1H, d, *J* 5.2 Hz, 9β-H), 4.70 (1H, dd, *J* 8.9 and 8.3 Hz, 17α-H), 6.82 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H), 6.87 (1H, d, *J* 2.5 Hz, 4-H) and 7.30 (1H, dd, *J* 8.5 and 1.0 Hz, 1-H); δ_C (100 MHz) 12.9 (13β-Me), 20.9 (17-OC(O)*C*H_3), 21.1

(3-OC(O)CH_3), 22.5 (C-15), 23.5 (C-7), 24.5 (C-6), 27.5 (C-16), 33.4 (C-8), 40.9 (C-14), 46.4 (C-13), 50.7 (C-12), 53.7 (C-9), 80.2 (C-17), 119.8 (C-2), 122.6 (C-4), 128.7 (C-1), 128.8 (C-10), 137.1 (C-5), 148.3 (C-3), 169.5 (3-O*C*(O)CH_3), 170.7 (17-O*C*(O)CH_3) and 211.6 (C-11).

Sodium borohydride reduction of 11-ketone 51

To a stirred solution of the 11-ketone **51** (310 mg, 0.9 mmol) in a mixture of THF (5 cm^3) and water (0.5 cm^3) was added sodium borohydride (200 mg, 5.3 mmol) and the mixture was stirred for 48h at 25°C. Water was added and the resulting mixture was extracted with chloroform. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (200 mg) which was dissolved in dry acetone (5 cm^3). Potassium carbonate (1 g) and dimethyl sulfate (0.5 cm^3) were added and the mixture was stirred for 18h at 25°C. Aqueous ammonia (1 cm^3) was added and the mixture was stirred for 30 min and then was extracted into ethyl acetate. The extract was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a mixture of products (244 mg) which was adsorbed onto silica gel (25 g) and eluted with ethyl acetate-toluene (1:9) to give 17β-acetoxy-3-methoxy-9β-estra-1,3,5(10)-triene-11β-ol **52** (84 mg, 28%), as an oil, (Found: M^+, 344. $C_{21}H_{28}O_4$ requires *M*, 344); ν_{max}/cm^{-1} 3571 (OH), 1716 (C=O); δ_H (200 MHz) 1.05 (3H, s, 13β-Me), 2.03 (3H, s, 17β-OAc), 2.40 (1H, br. d, *J* 10.6 Hz, 9β-H), 2.8 (2H, m, 6-H_2), 3.75 (3H, s, 3-OMe), 4.6-4.7 (2H, m, 11α- and 17α-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.16 (1H, d, *J* 8.6 Hz, 1-H), followed by 17β-acetoxy-3-methoxy-9β-estra-1,3,5(10)-triene-11α-ol **53** (136 mg, 46%), as an oil, (Found: M^+, 344. $C_{21}H_{28}O_4$ requires *M*, 344); ν_{max}/cm^{-1} 3604 (OH), 1723 (C=O); δ_H (200 MHz) 0.91 (3H, s, 13β-Me), 2.00 (3H, s, 17β-OAc), 2.65 (2H, m, 6-H_2), 3.11 (1H, t, *J* 2 x 4.5 Hz, 9β-H), 3.74 (3H, s, 3-OMe), 4.38 (1H, dt, *J* 8.1 and 4.5 Hz, 11α-H), 4.55 (1H, dd, *J* 8.9 and 7.2 Hz, 17α-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.66 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.86 (1H, d, *J* 8.6 Hz, 1-H).

3-Methoxy-16α-phenylsulfonyl-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate 56

A solution of 3-methoxy-16α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate **55** [57] (100 mg, 0.2 mmol) in ethyl acetate (6 cm^3) was shaken in the presence of palladium on charcoal (10%, 10 mg) under a hydrogen atmosphere (414 kPa) for 3h at 25°C. The catalyst was removed by filtration (Celite) and washed thoroughly with chloroform. The combined organic phase was concentrated under reduced pressure to afford the dihydro compound **56** (95 mg, 96%), m.p. 195-197°C (from benzene-hexane) (lit., [57] 199-200°C) (Found: M^+, 494. $C_{29}H_{34}O_5S$ requires *M*, 494); δ_H (200 MHz) 0.91 (3H, s, 13β-Me), 1.67 (3H, s, 17β-OAc), 3.76 (3H, s, 3-OMe), 4.38 (1H, ddd, *J* 11.8, 4.9 and 2.6 Hz, 16β-H), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H), 7.17 (1H, d, *J* 8.5 Hz, 1-H) and 7.5-8.0 (5H, m, 16α-SO_2Ph).

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol 59

a) A solution of 3-methoxy-16α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate **55** (7.6 g, 15.5 mmol) in chloroform (20 cm^3) was stirred with palladium on carbon (10%, 1 g) at 75°C under a hydrogen atmosphere (50 bar) for 72h. The cooled solution was filtered through Celite and evaporated to give a residue (8.2 g) which was dissolved in a mixture of acetic anhydride (10 cm^3) and THF (20 cm^3) and stirred with toluene-*p*-sulfonic acid (1 g) for 4h. Water and solid sodium hydrogen carbonate were added until effervescence ceased. The resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (satd. aq. $NaHCO_3$, water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give crude 3-methoxy-16α-phenylsulfonyl-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate **56** (8.4 g). This was dissolved in THF (150 cm^3) and was added to a solution of sodium (6 g, 260 mmol) in a mixture of liquid ammonia (800 cm^3; freshly distilled from sodium) and THF (50 cm^3) and the resulting mixture was stirred at -33°C for 2h. Solid ammonium chloride was added and the ammonia was removed by evaporation. The resultant mixture was diluted with water and extracted with chloroform. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (4.47 g). This was flash chromatographed on silica gel (120 g) with ethyl acetate-toluene (1:4) as eluent to give

3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17-ol **59** (3.4 g, 70%), m.p. 119-121°C (from methanol) (lit., [57] 120.5-121°C) (Found: M^+, 312. $C_{21}H_{28}O_2$ requires *M*, 312); δ_H (200 MHz) 0.88 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 6.60 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.20 (1H, d, *J* 8.5 Hz, 1-H).

b) A solution of 3-methoxy-16α-phenylsulfonyl-14,17α-ethenoestra-1,3,5(10)-trien-17β-yl acetate **55** (3.49 g, 7.1 mmol) in dry tetrahydrofuran (20 cm^3) was added slowly to a solution of sodium (1.8 g, 78 mmol) in liquid ammonia (freshly distilled from sodium; 400 cm^3) and dry tetrahydrofuran (50 cm^3). The solution was stirred at -33°C for 2h, then solid ammonium chloride (200 g) was added and the ammonia allowed to evaporate. The resulting mixture was extracted into chloroform, the combined organic phase was washed (brine), dried ($MgSO_4$) and evaporated under reduced pressure to afford 3-methoxy-14,17α-ethenoestra-1,3,5(10)-trien-17β-ol **57** (1.9 g, 87%), contaminated with 3-methoxy-14,17α-ethano-16α,17^1-cycloestra-1,3,5(10)-trien-17β-ol **58**.

A solution of the 14,17α-etheno compound **57** [(1.8 g, 5.8 mmol), containing **58**] in ethyl acetate (6 cm^3) was shaken under a hydrogen atmosphere (414 kPa) in the presence of palladium on charcoal catalyst (10%, 180 mg) for 5h at 25°C. The catalyst was removed by filtration through Celite and then washed with ethyl acetate. The combined organic phase was evaporated under reduced pressure to afford a residue (1.8 g). This was combined with a residue from a similar experiment (1.65 g) and recrystallised from methanol to give the 14,17α-ethano compound **59** (2.7 g, 78%). The mother liquor material was adsorbed onto silica gel (80 g) and eluted with ethyl acetate-toluene (1:9) to afford the 16α,17^1-cyclo compound **58** (300 mg, 9%) followed by another portion of the 14,17α-ethano compound **59** (394 mg, 11%).

14,17α-Ethanoestra-1,3,5(10)-triene-3,17β-diol 60

a) A solution of boron tribromide (1 mol dm^{-3} in dichloromethane, 5 cm^3, 5 mmol) was added to a solution of the 3-methyl ether **59** (500 mg, 1.6 mmol) in dichloromethane (10 cm^3) and the mixture was stirred at 25°C for 30 min. Water (50 cm^3) was added and the mixture was stirred for a further 10 min, poured into water (20 cm^3) and extracted with

ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and removed under reduced pressure to give a solid residue (485 mg). This was adsorbed onto silica gel (40 g) and eluted with methanol-chloroform (1:99) to give impure product (117 mg) followed by 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diol **60** (389 mg, 82%), m.p. 232-234°C (lit., [57] 240-241°C) (Found: M^+, 298; $C_{20}H_{26}O_2$ requires *M*, 298).

b) Diisobutylaluminium hydride (DIBAH) (1.5 mol dm^{-3} in toluene, 2.7 cm^3, 4 mmol) was added to solution of the 3-methyl ether **59** (298 mg, 0.96 mmol) in dry toluene (15 cm^3) and the mixture was refluxed for 24h. Hydrochloric acid (10%, 10 cm^3) was added to the cooled mixture and the product extracted into ethyl acetate. Chromatography of the residue after evaporation of the solvent (308 mg) on silica gel (30 g) with methanol-chloroform (1:19) afforded starting material **59** (19 mg) followed by the 3,17β-diol **60** (285 mg).

14,17α-Ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate 61

A solution of 3,17β-diol **60** (1.62 g) in a mixture of THF (20 cm^3) and acetic anhydride (2.5 cm^3, 23 mmol) was stirred with toluene-*p*-sulfonic acid (100 mg) for 18h at 25°C. Water and solid sodium hydrogen carbonate were added and once effervescence ceased the mixture was extracted into ethyl acetate. The combined organic phase was washed (satd. aq. $NaHCO_3$, water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (1.8 g). Flash chromatography on silica gel (50 g) with toluene afforded a mixture of the 3,17β-diacetate **61** and less polar impurities (404 mg, 22%) followed by the 3,17β-diacetate **61** (1.29 g, 70%), m.p. 137-141°C (from acetone-hexane); $[\alpha]_D$ +32° (*c* 0.8) (Found: C, 75.1; H, 8.0%; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.4; H, 7.9%; *M*, 382); ν_{max}/cm^{-1} 1727 (C=O); δ_H (400 MHz) 0.93 (3H, s, 13β-Me), 2.02 (3H, s, 17β-OAc), 2.28 (3H, s, 3-OAc), 2.65 (1H, td, *J* 2 x 11.5 and 4.2 Hz, 9α-H), 2.85 (2H, m, 6-H_2), 6.78 (1H, d, *J* 2.5 Hz, 4-H), 6.84 (1H, dd, *J* 8.4 and 2.5 Hz, 2-H) and 7.30 (1H, d, *J* 8.4 Hz, 1-H); δ_C (100 MHz) 14.0 (13β-Me), 21.1 (3-OC(O)*C*H_3), 21.6 (17β-OC(O)*C*H_3), 23.6 (C-7), 26.0 (C-11), 27.2 (C-17^2), 27.7 (C-12), 29.2 (C-17^1), 29.9 (C-6), 32.0 (C-15), 32.8 (C-16), 37.9 (C-8), 40.0 (C-9), 45.1 (C-14), 48.2 (C-13), 89.6 (C-17), 118.6 (C-2), 121.5 (C-4), 126.6 (C-1), 138.2 (C-10), 138.6 (C-5), 148.4 (C-3), 169.9 (17-O*C*(O)CH_3) and 171.0 (3-O*C*(O)CH_3).

14,17α-Ethanoestra-1,3,5(10),9(11)-tetraene-3,17β-diyl diacetate 62

A solution of the 3,17β-diol **60** (390 mg, 1.3 mmol) in dry methanol (60 cm^3) was stirred at 25°C while a solution of DDQ (320 mg, 1.4 mmol) in dry methanol was added over 2 min. The dark red solution was stirred at 40°C for 3h, during which time the colour faded to a light orange. The methanol was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (50 cm^3). This solution was washed [aq. K_2CO_3 (1 mol dm^{-3}), aq. Na_2SO_3 (2 mol dm^{-3}), aq. K_2CO_3 (1 mol dm^{-3}), water, brine]. The combined washings were extracted with ethyl acetate, and these extracts were combined with the original solution, and the resulting mixture was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (428 mg). This was dissolved in a mixture of pyridine (5 cm^3) and acetic anhydride (5 cm^3) and stirred with DMAP (20 mg) at 25°C for 24h. Water and solid sodium hydrogen carbonate were added, and once effervescence ceased the mixture was extracted with ethyl acetate. The combined organic phase was washed [satd. aq. $NaHCO_3$, aq. HCl (1 mol dm^{-3}), water, brine], dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (515 mg) which was adsorbed onto silica gel (50 g) and eluted with ethyl acetate-hexane (1:9) to give an inseparable mixture of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate **61** and 14,17α-ethanoestra-1,3,5(10),9(11)-tetraene-3,17β-diyl diacetate **62** (324 mg, *ca.* 65%), *m/z* 382 and 380; ν_{max} /cm^{-1} 1729 (C=O); δ_H (400 MHz) (**62**, *ca.* 65%) 0.93 (3H, s, 13β-Me), 2.03 (3H, s, 17β-OC(O)CH_3), 2.28 (3H, s, 3-OC(O)CH_3), 6.29 (1H, dt, *J* 5.4 and 2 x 2.7 Hz, 11-H), 6.80 (1H, d, *J* 2.5 Hz, 4-H), 6.85 (1H, dd, *J* 8.7 and 2.5 Hz, 2-H) and 7.66 (1H, d, *J* 8.7 Hz, 1-H); δ_H (400 MHz) (**61**, *ca.* 35%) 0.93 (3H, s, 13β-Me), 2.03 (3H, s, 17β-OC(O)CH_3), 2.28 (3H, s, 3-OC(O)CH_3), 6.78 (1H, d, *J* 2.5 Hz, 4-H), 6.84 (1-H, dd, *J* 8.5 and 2.5 Hz, 2-H) and 7.30 (1H, d, *J* 8.5 Hz, 1-H).

Dehydrogenation of 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol 59

To a stirred solution of 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol **59** (2.7 g, 8.7 mmol) in dry methanol (430 cm^3) at 25°C was added DDQ (2 g, 8.8 mmol) in methanol (25 cm^3) over a period of 2 min. After stirring for 1 h, during which time the solution faded from a deep red to a pale orange, the methanol was evaporated under reduced pressure and the residue was triturated with hot chloroform (50 cm^3) and then allowed to stand at 4°C for 16h. After stirring with activated charcoal for 5 min the solution was filtered through Celite to give a pale yellow solution which was concentrated under reduced pressure to give a residue (3.74 g) which was adsorbed onto alumina (activity III, 100 g) and eluted with ethyl acetate-toluene (3:17) to give an inseparable mixture of starting material **59** and 3-methoxy-14,17α-ethanoestra-1,3,5(10),9(11)-tetraen-17β-ol **63** (2.7 g), *m/z* 312 and 310; δ_H (200 MHz) (**59** *ca.* 50%) 0.89 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 6.6-6.8 (2H, m, 2- and 4-H) and 7.20 (1H, d, *J* 8.5 Hz, 1-H); δ_H (200 MHz) (**63** *ca.* 50%) 0.89 (3H, s, 13β-Me), 3.76 (3H, s, 3-OMe), 6.20 (1H, m, 11-H), 6.6-6.8 (2H, m, 2- and 4-H) and 7.60 (1H, d, *J* 8.8 Hz, 1-H).

3-Methoxy-14α,17α-ethanoestra-1,3,5(10),6,8,11-hexaen-17β-ol 64

A solution of 3-methoxy-14α,17α-ethanoestra-1,3,5(10)-trien-17β-ol **59** (270 mg, 0.9 mmol) and toluene-*p*-sulfonic acid (300 mg, 1.74 mmol) in dry methanol (50 cm^3) was stirred at 25°C while a solution of DDQ (400 mg, 1.76 mmol) in dry methanol (5 cm^3) was added in a dropwise fashion. The reaction was stirred for 18h at 25°C followed by 2h at reflux. The solvent was removed under reduced pressure and the residue was dissolved in chloroform (20 cm^3). This solution was washed (satd. aq. $NaHCO_3$), dried ($MgSO_4$) and evaporated to give a residue (220 mg). Chromatography on silica gel (25 g) with ethyl acetate-toluene (1:9) as eluent gave the *hexaene* **64** (154 mg, 58%), m.p. 198-200°C (from methanol); $[\alpha]_D$ -31° (*c* 0.2) (Found: C, 82.4; H, 7.5; M^+, 306. $C_{21}H_{22}O_2$ requires C, 82.3; H, 7.2; *M*, 306), ν_{max} /cm^{-1} 3609, 3464 (OH); δ_H (200 MHz) 0.85 (3H, s, 13β-Me), 1.70 (1H, s, D_2O exch., 17β-OH), 3.92 (3H, s, 3-OMe), 6.65 (1H, d, *J* 9.8 Hz, 12-H), 7.12 (1H, d, *J* 2.7 Hz, 4-H), 7.15 (1H, d, *J* 9.8 Hz, 11-H), 7.18 (1H, dd, *J* 9.3 and 2.7 Hz, 2-H), 7.21 (1H, d, *J* 8.3 Hz, 7-H), 7.64 (1H, d, *J* 8.3 Hz, 6-H) and 8.60 (1H, d, *J* 9.3 Hz, 1-H).

3-Methoxy-14,17α-ethanoestra-1,3,5(10),6,8-pentaen-17β-ol 65

A solution of the hexaene **64** (140 mg, 0.5 mmol) in ethyl acetate (5 cm^3) was stirred with palladium on carbon (10%, 10 mg) under hydrogen at 25°C for 4h. The catalyst was filtered off (Celite) and the residue after evaporation of the solvent (137 mg) was chromatographed on silica gel (12 g) with ethyl acetate-toluene (1:9) to give a non-steroidal impurity (35 mg) followed by the *pentaene* **65** (53 mg, 37%), m.p. 130-131°C (from methanol); $[\alpha]_D$ +29° (*c* 0.1) (Found: C, 81.8; H, 7.9; M^+, 308. $C_{21}H_{24}O_2$ requires C, 81.8; H, 7.8; *M*, 308); ν_{max} /cm^{-1} 3600, 3425 (OH); δ_H (200 MHz) 0.92 (3H, s, 13β-Me), 1.65 (1H, s, D_2O exch., 17β-OH), 3.92 (3H, s, 3-OMe), 7.12 (1H, d, *J* 2.4 Hz, 4-H), 7.18 (1H, dd, *J* 9.1 and 2.4 Hz, 2-H), 7.20 (1H, d, *J* 8.5 Hz, 7-H), 7.57 (1H, d, *J* 8.5 Hz, 6-H) and 7.92 (1H, d, *J* 9.1 Hz, 1-H).

Reaction of 14,17α-Ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate 61 with dimethyldioxirane

A solution of the 3,17β-diacetate **61** (104 mg, 0.3 mmol) in freshly prepared DMD (0.1 mol dm^{-3} in acetone, 8 cm^3, 0.8 mmol) was stirred for 48h at 25°C. The acetone was removed under reduced pressure to give a residue (100 mg) which was adsorbed onto silica gel (10 g) and eluted with ethyl acetate toluene (1:9) to give starting material **61** (20 mg, 20%), an impure product (40 mg) and a complex mixture of polar products (*ca* 40 mg). The impure product was rechromatographed on silica gel (5 g) with ethyl acetate-toluene (1:19) as eluent to give 6-*oxo*-14,17α-*ethanoestra*-1,3,5(10)-*triene*-3,17β-*diyl diacetate* **66** (18 mg, 16%), m.p. 169-172°C (from methanol); $[\alpha]_D$ -17° (*c* 0.5) (Found: M^+, 396.195 $C_{24}H_{28}O_5$ requires *M*, 396.194); ν_{max}/cm^{-1} 1728, 1681 (C=O); δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 2.03, (3H, s, 17β-OAc), 2.31 (3H, s, 3-OAc), 7.27 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H), 7.48 (1H, d, *J* 8.5 Hz, 1-H) and 7.75 (1H, d, *J* 2.6 Hz, 4-H); δ_C (50 MHz) 13.7 (13β-Me), 21.0 (3-OC(O)*C*H_3), 21.5 (17β-OC(O)*C*H_3), 25.3 (C-7), 27.2 (C-11), 27.6 (C-12), 29.2 (C-17^2), 31.8 (C-17^1), 32.3 (C-15), 37.7 (C-16), 40.3 (C-8), 41.4 (C-9), 44.7 (C-14), 48.0 (C-13), 89.2 (C-17), 120.0 (C-2), 126.9 (C-1 and C-4), 133.5 (C-10), 145.0 (C-5), 149.2 (C-3), 169.4 (17β-O*C*(O)CH_3), 170.8 (3-O*C*(O)CH_3) and 197.1 (C-6).

14,17α-Ethano-9β-estra-1,3,5(10)-triene-3,17β-diyl diacetate 67

a) A solution of 14,17α-Ethanoestra-1,3,5(10),9(11)-tetraene-3,17β-diyl diacetate **62** (contaminated with **61**) (324 mg, 0.9 mmol) in THF (10 cm^3) and ethanol (10 cm^3) was stirred with Raney nickel (Aldrich W-2, 10 cm^3) at 50°C under a hydrogen atmosphere (50 bar) for 48h. The cooled solution was filtered through Celite, the catalyst was washed thoroughly with ethyl acetate and chloroform. The residue after evaporation of the solvent (272 mg) was adsorbed onto silica gel (35g) and eluted with ethyl acetate-toluene (1:99) to give 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate **61** (121 mg, 37%), m.p. 138-140°C (from acetone-hexane), mixed fractions (109 mg), and 14,17α-*ethano*-9β-*estra*-1,3,5(10)-*triene*-3,17β-*diyl diacetate* **67** (27 mg, 9%), m.p. 106-109°C (from isopropanol); $[\alpha]_D$ +46° (*c* 0.4) (Found: C, 75.2; H, 8.0; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.4; H, 7.9; *M*, 382); ν_{max}/cm^{-1} 1750, 1727 (C=O); δ_H (400 MHz) 0.94 (1H, ddd, *J* 13, 9.8 and 5.2 Hz, 17^2_n-H), 1.03 (3H, s, 13β-Me), 1.16 (1H, dt, *J* 13 and 2 x 3.5 Hz, 17^2_x-H), 1.99 (3H, s, 17β-OAc), 2.27 (3H, s, 3-OAc), 2.44 (1H, br. d, *J* 15 Hz, 11α-H), 2.55 (1H, ddd, *J* 15, 11 and 5.6 Hz, 6α-H), 2.66 (1H, dt, *J* 15 and 2 x 5.2 Hz, 6β-H), 2.84 (1H, br. t, *J* 2 x 6.2 Hz, 9β-H), 6.82 (1H, d, *J* 2.5 Hz, 4-H), 6.89 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H) and 7.31 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) 14.2 (13β-Me), 21.2 (3-OC(O)*C*H_3), 21.6 (17β-OC(O)*C*H_3), 21.8 (C-11), 23.2 (C-7), 24.5 (C-12), 28.4 (C-6), 28.8 ($C\text{-}17^2$), 29.1 ($C\text{-}17^1$), 31.8 (C-16), 33.8 (C-15), 34.3 (C-9), 35.3 (C-8), 45.2 (C-14), 48.7 (C-13), 89.8 (C-17), 118.8 (C-2), 120.3 (C-4), 124.5 (C-1), 139.3 (C-10), 141.2 (C-5), 148.1 (C-3), 169.7 (17β-O*C*(O)CH_3) and 170.9 (3-O*C*(O)CH_3); δ_H (400 MHz, C_6D_6) 0.68 (1H, ddd, *J* 12.6, 9.9 and 5.1 Hz, 17^2_n-H), 0.92 (3H, s, 13β-Me), 1.00 (1H, m, 7β-H), 1.28 (1H, dt, *J* 12.6 and 2 x 4.1 Hz, 12β-H), 1.46 (1H, m, 17^1_n-H), 1.65 (3H, s, 17β-OAc), 1.76 (3H, s, 3-OAc), 2.44 (1H, br. t, *J* 2 x 6.7 Hz, 9β-H), 6.88 (1H, d, *J* 2.3 Hz, 4-H), 6.93 (1H, dd, *J* 8.3 and 2.3 Hz, 2-H) and 7.07 (1H, d, *J* 8.3 Hz, 1-H); δ_C (100 MHz, C_6D_6) 14.4 (13β-Me), 20.6 (3-OC(O)*C*H_3), 21.1 (17β-OC(O)*C*H_3), 22.0 (C-11), 23.4 (C-7), 25.0 (C-12), 28.6 (C-6), 28.9 ($C\text{-}17^2$), 29.4 ($C\text{-}17^1$), 32.3 (C-16), 33.9 (C-15), 34.4 (C-9), 35.4 (C-8), 45.4 (C-14), 48.9 (C-13), 89.7 (C-17), 119.4 (C-2), 120.8 (C-4), 124.5 (C-1), 139.2 (C-10), 141.2 (C-5), 149.1 (C-3), 168.6 (17β-O*C*(O)CH_3) and 169.8 (3-O*C*(O)CH_3). The mixed fractions were

rechromatographed on silica gel (15 g) eluting with ethyl acetate-toluene (1:99) to give further **61** (50 mg, 15%) and **67** (33 mg, 10%).

b) To a solution of the $\Delta^{9(11)}$ 3,17β-diacetate **62** (contaminated with **61**) (37 mg, 0.1 mmol) in dichloromethane (5 cm^3) at 25°C was added triethylsilane (0.5 cm^3) followed by trifluoroacetic acid (2 cm^3). The mixture was stirred at 25°C for 168h, with further triethylsilane (0.5 cm^3) and trifluoroacetic acid (2ml) being added after 72h. The solution was then poured into saturated aqueous sodium hydrogen carbonate (50 cm^3) and extracted into ethyl acetate. The combined organic phase was washed (satd. aq. $NaHCO_3$, water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (56 mg). Chromatography on silica gel (5 g) with ethyl acetate-toluene (1:99) gave 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate **61** (19 mg, 50%) followed by 14,17α-ethano-9β-estra-1,3,5(10)-triene-3,17β-diyl diacetate **67** (4 mg, 10%).

14α,17α-Ethano-9β-estra-1,3,5(10)-triene-3,17β-diol 68

A solution of the 3,17β-diacetate **67** (46 mg, 0.1 mmol) in methanolic potassium hydroxide (1%, 10 cm^3) was stirred for 24h at 25°C. Water was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (40 mg) which was chromatographed on silica gel (5 g) with ethyl acetate-toluene (1:4) as eluent to give the 3,17β-*diol* **68** (33 mg, 91%), m.p. 208-209°C (from chloroform); $[\alpha]_D$ +48° (*c* 0.5) (Found: M^+, 298.192. $C_{20}H_{26}O_2$ requires *M*, 298.193); ν_{max}/cm^{-1} 3692, 3599, 3352 br. (OH).

Epoxidation-rearrangement of 14,17α-Ethanoestra-1,3,5(10),9(11)-tetraene-3,17β-diyl diacetate 62

A solution of the $\Delta^{9(11)}$ 3,17β-diacetate **62** (contaminated with **61**) (450 mg, 0.8 mmol) in dichloromethane (5 cm^3) was stirred at 25°C while a solution of dimethyldioxirane (*ca* 0.1 mol dm^{-3} in acetone, 25 cm^3, 2.5 mmol) was added, and the resulting mixture was stirred for 75 min at 25°C. The solvent was removed under reduced pressure to give a residue (500 mg) which was dissolved in benzene (15 cm^3) and refluxed with lithium

perchlorate (100 mg) for 1h. The cooled solution was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (456 mg). Flash chromatography on silica gel (50 g) with ethyl acetate-hexane (1:4) as eluent gave 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate (149 mg, 33%) followed by a mixture of 11-ketones **69** and **70** (220 mg, 46%). Recrystallisation of a portion of this mixture from acetone-hexane afforded 11-*oxo*-14α,17α-*ethanoestra*-1,3,5(10)-*triene*-3,17β-*diyl diacetate* **69**, m.p. 157-160°C; $[\alpha]_D$ +220° (*c* 0.1) (Found: C, 72.3; H, 7.2%; M^+, 396. $C_{24}H_{28}O_5$ requires C, 72.7; H, 7.1%; *M*, 396); ν_{max}/cm^{-1} 1732 (C=O); δ_H (400 MHz) 1.03 (3H, d, *J* 0.8 Hz, 13β-Me), 1.53 (1H, qd, *J* 3 x 12.8 and 5.8 Hz, 7α-H), 1.84 (1H, m, 7β-H), 1.98 (1H, td, *J* 2 x 12.8 and 2.2 Hz, 8β-H), 2.02 (3H, s, 17β-OAc), 2.23 (1H, d, *J* 12.8 Hz, 12β-H), 2.27 (3H, s, 3-OAc), 2.77 (1H, dd, *J* 12.8 and 0.8 Hz, 12α-H), 2.84 (2H, m, 6-H_2), 3.89 (1H, d, *J* 12.8 Hz, 9α-H), 6.81 (1H, d, *J* 2.4 Hz, 4-H), 6.89 (1H, dd, *J* 8.7 and 2.4 Hz, 2-H) and 7.40 (1H, d, *J* 8.7 Hz, 1-H); δ_C (100 MHz) 14.6 (13β-Me), 21.1 (3-OC(O)*C*H_3), 21.4 (17β-OC(O)*C*H_3), 24.3 (C-7), 27.7 (C-17^2), 29.5 (C-17^1), 30.1 (C-6), 31.8 (C-15), 32.2 (C-16), 42.5 (C-8), 45.4 (C-14), 47.1 (C-12), 50.1 (C-9), 54.3 (C-13), 88.1 (C-17), 118.6 (C-2), 121.6 (C-4), 129.2 (C-10), 131.6 (C-1), 138.4 (C-5), 148.9 (C-3), 169.6 (17β-O*C*(O)CH_3), 170.9 (3-O*C*(O)CH_3) and 209.2 (C-11).

Sodium borohydride reduction of 11-ketones 69 and 70

Sodium borohydride (200 mg, 5 mmol) was added to a solution of the total product mixture obtained from the previous experiment (**69** and **70**) (200 mg, 0.5 mmol) in a mixture of THF (2 cm^3) and methanol (2 cm^3) and the mixture was stirred for 18h at 25°C. Water was added and the resulting mixture was extracted with ethyl acetate followed by chloroform. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (188 mg) which was dissolved in dry acetone and stirred with potassium carbonate (1 g) and dimethyl sulfate (1 cm^3) for 18h at 25°C. Ammonia (25%, 3ml) was added and the mixture was stirred for 30 min. Water was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (170 mg) which was chromatographed on silica gel (20 g) with ethyl acetate-toluene (1:9) as eluent to give 17β-*acetoxy*-3-*methoxy*-14α,17α-*ethanoestra*-1,3,5(10)-*trien*-11β-*ol* **71**

(106 mg, 56%), m.p. 193-194°C (from methanol); $[\alpha]_D$ +92° (*c* 0.5) (Found: C, 74.5; H, 8.3%; M^+, 370. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.2%; *M*, 370); ν_{max}/cm^{-1} 3573 (OH), 1728 (C=O); δ_H (400 MHz) 1.19 (3H, s, 13β-Me), 1.56 (1H, s, D_2O exch., 11β-OH), 2.02 (3H, s, 17β-OAc), 2.77-2.96 (3H, m, 6-H_2 and 9α-H), 4.75 (1H, q *J* 3.2 Hz, 11α-H), 6.67 (1H, d, *J* 2.6 Hz, 4-H), 6.77 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H) and 7.23 (1H, d, *J* 8.5 Hz, 1-H) followed by 17β-acetoxy-3-methoxy-14α,17α-ethano-9β-estra-1,3,5(10)-trien-11α-ol **72** (21 mg, 11%), as an oil, (Found: M^+, 370. $C_{23}H_{30}O_4$ requires *M*, 370); ν_{max}/cm^{-1} 3691, 3600 (OH), 1727 (C=O); δ_H (400 MHz) 0.94 (1H, m, 17^2_n-H), 1.09 (3H, s, 13β-Me), 2.54 (1H, td, *J* 2 x 13.2 and 5.1 Hz, 6α-H), 2.65 (1H, ddd, *J* 13.2, 4.7 and 2.9 Hz, 6β-H), 3.11 (1H, dd, *J* 7.3 and 5.3 Hz, 9β-H), 3.78 (3H, s, 3-OMe), 4.57 (1H, dt, *J* 8.8 and 2 x 5.3 Hz, 11β-H), 6.68 (1H, d, *J* 2.6 Hz, 4-H), 6.72 (1H, dd, *J* 8.3 and 2.6 Hz, 2-H) and 7.67 (1H, d, *J* 8.3 Hz, 1-H).

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-triene-11β,17β-diol 73

A solution of the 17β-acetate **71** (11 mg, 0.03 mmol) in a mixture of methanolic potassium hydroxide (1%, 1 cm^3) and THF (0.5 cm^3) was stirred at 25°C for 22h. Water was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (10 mg) which was recrystallised from methanol to give the 11β,17β-*diol* **73**, m.p. 193-194°C; $[\alpha]_D$ +105° (*c* 1.2) (Found: C, 77.0; H, 8.5%; M^+, 328. $C_{21}H_{28}O_3$ requires C, 76.8; H, 8.6%; *M*, 328); ν_{max} /cm^{-1} 3685, 3598 (OH); δ_H (400 MHz) 1.16 (3H, s, 13β-Me), 1.33 (1H, qd, *J* 3 x 12 and 5.6 Hz, 7α-H), 1.51-1.54 (2H, 2 x s, D_2O exch, 11β-, 17β-OH), 1.88 (1H, td, *J* 2 x 12 and 2.3Hz, 8β-H), 2.82 (2H, m, 6-H_2), 2.89 (1H, dd, *J* 12 and 3.3 Hz, 9α-H), 3.78 (3H, s, 3-OMe), 4.75 (1H, q, *J* 3.3 Hz, 11α-H), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.76 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.22 (1H, d, *J* 2.7 Hz, 1-H); δ_C (100 MHz) 16.3 (13β-Me), 23.4 (C-7), 26.3 (C-17^2), 30.4 (C-6), 32.2 (C-15), 33.3 (C-17^1), 35.5 (C-16), 33.0 (C-12), 35.2 (C-8), 43.4 (C-9), 46.4 (C-13), 47.7 (C-14), 55.2 (3-OMe), 67.3 (C-11), 84.3 (C-17), 112.4 (C-2), 114.7 (C-4), 126.3 (C-1), 128.2 (C-10), 139.9 (C-5) and 157.7 (C-3).

3-Methoxy-14,17α-ethano-9β-estra-1,3,5(10)-triene-11α,17β-diyl diacetate 74

A solution of the 11α-alcohol **72** (20 mg, 0.05 mmol) in a mixture of pyridine (1 cm^3) and acetic anhydride (1 cm^3) was stirred with catalytic DMAP for 30 min at 25°C. Saturated aqueous sodium hydrogen carbonate was added and once the effervescence ceased the mixture was extracted into ethyl acetate. The combined organic phase was washed [satd. aq. $NaHCO_3$, aq. HCl (1 mol dm^{-3}), water, brine], dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (28 mg) which was chromatographed on silica gel (5 g) with ethyl acetate-toluene (1:9) as eluent to give the 11α,17β-*diacetate* **74** (15 mg, 74%), as an oil, $[\alpha]_D$ +57° (*c* 1.5) (Found: M^+, 412.256. $C_{25}H_{32}O_5$ requires *M*, 412.255); ν_{max}/cm^{-1} 1724 (C=O); δ_H (400 MHz) 0.86 (1H, m, 17^2_n-H), 1.13 (3H, s, 13β-Me), 1.70 (1H, dd, *J* 12.3 and 4.2 Hz, 12β-H), 2.49 (1H, td, *J* 2 x 13.3 and 5.2 Hz, 6α-H), 2.58 (1H, ddd, *J* 13.3, 4.8 and 2.8 Hz, 6β-H), 3.21 (1H, t, *J* 2 x 6.3 Hz, 9β-H), 3.78 (3H, s, 3-OMe), 5.58 (1H, ddd, *J* 12.1, 5.6 and 4.8 Hz, 11β-H), 6.69 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.61 (1H, d, *J* 8.5 Hz, 1-H).

3-Methoxy-11-oxo-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate 75

To a solution of 17β-acetoxy-3-methoxy-14α,17α-ethanoestra-1,3,5(10)-trien-11β-ol **71** (94 mg, 0.3 mmol) in dichloromethane (5 cm^3) was added Dess-Martin periodinane [72] (120 mg, 0.33 mmol) and the mixture was stirred for 60 min. Diethyl ether (20 cm^3) was added, and the resulting mixture was poured into a saturated aqueous sodium hydrogen carbonate solution (30 cm^3) with sodium thiosulfate (2 g) dissolved in it and the resulting mixture was extracted into diethyl ether. The combined organic phase was washed (satd. aq. $NaHCO_3$, water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to gave a residue (95 mg). A portion of this (75 mg) was chromatographed on silica gel (1 g) with diethyl ether-hexane (3:7) as eluent to give the 11-*ketone* **75** (59 mg, 68%), m.p. 135-138°C (from diisopropyl ether); $[\alpha]_D$ +239° (*c* 0.4) (Found: C, 75.0; H, 7.8%; M^+, 368. $C_{23}H_{28}O_4$ requires C, 75.0; H, 7.7%; *M*, 368); ν_{max}/cm^{-1} 1729, 1711 (C=O); δ_H (400 MHz) 0.90 (3H, d, *J* 0.8 Hz, 13β-Me), 1.52 (1H, qd, *J* 3 x 12.2 and 5.6 Hz, 7α-H), 1.98 (1H, td, *J* 2 x 12.2 and 2.0 Hz, 8β-H), 2.01 (3H, s, 17β-OAc), 2.22 (1H, d, *J* 12.0 Hz, 12β-H), 2.36 (1H, tt, *J* 2 x 12.7 and 2 x 3.7 Hz, 17^2_x-H), 2.76 (1H, dd, *J* 12.0 and 0.8 Hz, 12α-H), 2.80

(2H, m, 6-H_2), 3.88 (1H, d, *J* 12.2 Hz, 9α-H), 3.76 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.9 Hz, 4-H), 6.75 (1H, dd, *J* 8.8 and 2.9 Hz, 2-H) and 7.30 (1H, d, *J* 8.8 Hz, 1-H); δ_C (100 MHz) 14.7 (13β-Me), 21.4 (17β-OC(O)*C*H_3), 24.7 (C-7), 27.8 (C-17^2), 29.6 (C-17^1), 30.4 (C-6), 31.8 (C-15), 32.2 (C-16), 42.8 (C-8), 45.4 (C-14), 47.0 (C-12), 50.0 (C-9), 54.4 (C-13), 55.2 (3-O*Me*), 88.1 (C-17), 111.6 (C-2), 113.8 (C-4), 123.8 (C-10), 131.5 (C-1), 138.2 (C-5), 157.9 (C-3), 170.7 (17β-O*C*(O)CH_3) and 209.7 (C-11). The remainder of the crude product (20 mg) was treated with sodium borohydride (200 mg) in a mixture of THF (2 cm^3) and methanol (2 cm^3) for 30 min at 25°C. Water was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (17 mg) which was recrystallised from methanol to give 17β-acetoxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-11β-ol **71**, m.p. 190-192°C (from methanol); $[\alpha]_D$ +90° (*c* 0.5).

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-triene-11α,17β-diol 76

Borane-dimethyl sulfide complex (10 mol dm^{-3}, 10 cm^3, 100 mmol) was added slowly to a stirred solution of 3-methoxy-14,17α-ethanoestra-1,3,5(10),9(11)-tetraen-17β-ol **63** (contaminated with **59**) (2.7 g, *ca.* 8.7 mmol) in dry tetrahydrofuran (150 cm^3) at 25°C. The mixture was refluxed for 72h, with a further aliquot of borane being added after 24h. After cooling to 0°C, hydrogen peroxide (100 vol, 20 cm^3) and aqueous sodium hydroxide (4 mol dm^{-3}, 20 cm^3) were added cautiously and the mixture was stirred for 18h at 25°C. Water (80 cm^3) was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$) and evaporated to give a residue (*ca* 3 g) which was adsorbed onto silica gel (150 g) and eluted with ethyl acetate-toluene (1:9) to give 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-ol **59** (958 mg, 35%), followed by an unidentified, non-steroidal product (400 mg). Further elution with ethyl acetate-toluene (3:2) afforded the 11α,17β-diol **76** (888 mg, 31%), as an oil, (Found: M^+, 328. $C_{21}H_{28}O_3$ requires *M*, 328); ν_{max}/cm^{-1} 3597, 3457 br. (OH); δ_H (200 MHz) 0.89 (3H, s, 13β-Me), 2.48 (1H, t, *J* 2 x 10 Hz, 9α-H), 2.76 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.20 (1H, td, *J* 2 x 10 and 5.8 Hz, 11β-H), 6.64 (1H, d, *J* 2.8 Hz, 4-H), 6.74 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.88 (1H, d, *J* 8.7 Hz, 1-H); δ_C (50 MHz) 14.4 (13β-Me), 23.0 (C-7), 27.0 (C-17^2), 29.1 (C-6), 32.1 (C-15), 32.9 (C-17^1), 35.3 (C-16), 38.0 (C-8), 39.5 (C-12),

45.4 (C-9), 46.8 (C-13), 48.1 (C-14), 55.2 (3-OMe), 71.2 (C-11), 83.8 (C-17), 111.1 (C-2), 113.7 (C-4), 127.5 (C-1), 132.9 (C-10), 139.1 (C-5) and 157.7 (C-3).

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-triene-11α,17β-diyl diacetate 77

To a solution of the 11α,17β-diol **76** (160 mg, 0.5 mmol) in pyridine (5 cm^3) at 25°C was added acetic anhydride (0.2 cm^3, 2.2 mmol) and DMAP (10 mg). The mixture was stirred for 16h at 25°C, water was then added and the solution was extracted with ethyl acetate. The combined organic phase was washed [aq. HCl (3 mol dm^{-3}), satd. aq. $NaHCO_3$, brine], dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (196 mg) which was adsorbed onto silica gel (20 g) and eluted with ethyl acetate-toluene (1:9) to give the 11α,17β-*diacetate* **77** (150 mg, 74%), m.p. 156-157 °C (from methanol); $[\alpha]_D$ -101° (*c* 0.9) [Found: C, 72.8; H, 7.7%; M^+, 352 (*M*-HOAc). $C_{25}H_{32}O_5$ requires C, 72.8; H, 7.8%; *M*, 412]; ν_{max}/cm^{-1} 1724 (C=O); δ_H (200 MHz) 0.92 (3H, s, 13β-Me), 1.93 and 2.03 (both 3H, s, 11α-OAc and 17β-OAc), 2.70 (3H, m, 9α-H, 6-H_2), 3.70 (3H , s, 3-OMe), 5.30 (1H, td, *J* 2 x 10.5 and 5.6 Hz, 11β-H), 6.62 (2H, m, 2-H and 4-H) and 6.95 (1H, d, *J* 9.4 Hz, 1-H); δ_C (50 MHz) 14.5 (13β-Me), 21.4 and 21.7 (11α-, 17β-OC(O)*C*H_3), 22.8 (C-7), 27.8 (C-17^2), 28.7 (C-17^1), 29.2 (C-6), 32.0 (C-15), 32.4 (C-16), 33.5 (C-12), 39.0 (C-8), 41.2 (C-9), 44.7 (C-13), 49.2 (C-14), 55.1 (3-OMe), 74.1 (C-11), 89.1 (C-17), 111.1 (C-2), 113.8 (C-4), 125.3 (C-1), 132.2 (C-10), 139.3 (C-5), 157.8 (C-3), 170.7 and 170.8 (11α-, 17β-O*C*(O)CH_3).

14,17α-Ethanoestra-1,3,5(10)-triene-3,11α,17β-triol 78

A solution of the 11α,17β-diacetate **77** (150 mg, 0.4 mmol), chlorotrimethylsilane (0.05 cm^3; 0.4 mmol) and sodium iodide (60 mg, 0.4 mmol) in dry acetonitrile (5 cm^3) was stirred for 18h at 25°C, followed by 8h at reflux. Water (10 cm^3) was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (satd. aq. $Na_2S_2O_3$, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (150 mg) which was dissolved in methanolic potassium hydroxide (1%, 20 cm^3) and was stirred for 50h at 25°C. Saturated aqueous ammonium chloride was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (brine),

dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (120 mg) which was adsorbed onto silica gel (12 g) and eluted with methanol-chloroform (1:9) to give the 3,11α,17β-*triol* **78** (74 mg, 65%), m.p. 257-260°C (from ethyl acetate); $[\alpha]_D$ -65° (*c* 0.8 in THF) (Found: M^+, 314.188. $C_{20}H_{26}O_3$ requires *M*, 314.188).

17β-Hydroxy-3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-11-one 79

A solution of DMSO (0.7 cm^3, 9 mmol) in dry dichloromethane (5 cm^3) was added to a solution of oxalyl chloride (2 mol dm^{-3} in dichloromethane, 1.5 cm^3, 3 mmol) at -78°C. After stirring for 5 min at -78°C, 3-methoxy-14,17α-ethanoestra-1,3,5(10)-triene-11α,17β-diol **76** (780 mg, 2.4 mmol) in dry dichloromethane (10 cm^3) was added and the mixture stirred for 20 min at -78°C. Triethylamine (1.7 cm^3, 12 mmol) was added and the mixture allowed to warm to 25°C. Water (20 cm^3) was added and the mixture extracted with dichloromethane. The combined organic phase was washed [aq. HCl (3 mol dm^{-3}), water, satd. aq. Na_2CO_3, water), dried ($MgSO_4$) and evaporated to give a residue (600 mg) which was adsorbed onto silica gel (80 g) and eluted with ethyl acetate-toluene (1:4) under pressure to give the 11-ketone **79** (450 mg, 58%), as an oil (Found: M^+, 326. $C_{21}H_{26}O_3$ requires *M*, 326); ν_{max}/cm^{-1} 1709 (C=O); δ_H (200 MHz) 0.79 (3H, s, 13β-Me), 3.70 (3H, s, 3-OMe), 3.80 (1H, d, *J* 12 Hz, 9α-H), 6.55 (1H, d, *J* 2.6 Hz, 4-H), 6.69 (1H, dd, *J* 8.5 and 2.6 Hz, 2-H) and 7.22 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 14.2 (13β-Me), 24.2 (C-7), 27.1 (C-17^2), 30.3 (C-6), 31.4 (C-15), 33.1 (C-17^1), 35.5 (C-16), 43.4 (C-8), 46.5 (C-12), 47.3 (C-13), 50.0 (C-9), 53.4 (C-14), 55.2 (3-OMe), 82.9 (C-17), 111.5 (C-2), 113.8 (C-4), 123.9, 131.5 (C-1, C-10), 138.2 (C-5), 157.9 (C-3) and 210.3 (C-11).

Treatment of the 11-ketone **79** with hydrochloric acid (10 mol dm^{-3}, 0.2 cm^3) in methanol (5 cm^3) at reflux for 15 min [54] afforded unchanged material **79**.

Treatment of the 11-ketone **79** with piperidine at reflux for 15 min, [54] or with methanolic potassium hydroxide (1%) at reflux for 1h [100] afforded a complex mixture of products.

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-triene-11β,17β-diol 73

LAH (1 g, 26 mmol) was added to a solution of the 11-ketone **79** (513 mg, 1.6 mmol) in THF (20 cm^3) and the mixture was stirred for 1h at 25°C. Ethyl acetate (20 cm^3) was added and once effervescence ceased (10 min) the mixture was extracted with ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (424 mg) which was flash chromatographed on silica gel (50 g) with ethyl acetate-toluene (1:4) affording an unidentified product (72 mg) followed by the 11β,17β-diol **73** (280 mg, 54%), identical in all respects with that synthesised previously.

11-Oxo-14,17α-ethanoestra-1,3,5(10),6,8-pentaene-3,17β-diyl diacetate 80

To a solution of 14,17α-ethanoestra-1,3,5(10)-triene-3,17β-diyl diacetate **61** (1.29 g, 3.3 mmol) in a mixture of acetic acid (90 cm^3) and water (10 cm^3) was added ceric ammonium nitrate (16.3 g, 29.7 mmol) and the mixture was stirred for 1 h at 25°C. Ice and solid sodium hydrogen carbonate were added, and once effervescence ceased the mixture was extracted into diethyl ether. The combined organic phase was washed (satd. aq. $NaHCO_3$, water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude residue (1.18 g) which was adsorbed onto silica gel (100 g) and eluted with ethyl acetate-toluene (1:19) to give the 11-*ketone* **80** (740 mg, 57%), m.p. 157-160 °C (from methanol); $[\alpha]_D$ -46° (*c* 0.5) (lit., [123] m.p. 169-170°C $[\alpha]_D$ -48°) (Found: M^+, 392. $C_{24}H_{24}O_5$ requires *M*, 392); ν_{max}/cm^{-1} 1755, 1731 (C=O); δ_H (200 MHz) 0.99 (3H, d, *J* 1.2 Hz, 13β-Me), 2.06 (3H, s, 17β-OAc), 2.34 (3H, s, 3-OAc), 2.61 (1H, d, *J* 18 Hz, 12β-H), 3.20 (1H, dd, *J* 18 and 1.2 Hz, 12α-H), 7.32 (1H, d, *J* 8.5 Hz, 7-H), 7.36 (1H, dd, *J* 9.5 and 2.5 Hz, 2-H), 7.55 (1H, d, *J* 2.5 Hz, 4-H), 7.95 (1H, d, *J* 8.5 Hz, 6-H) and 9.41 (1H, d, *J* 9.5 Hz, 1-H); δ_C (50 MHz) 16.1 (13β-Me), 21.2 (3-OC(O)*C*H_3), 21.4 (17β-OC(O)*C*H_3), 31.2 (C-17^2), 31.7 (C-17^1), 32.3 (C-15), 39.9 (C-16), 45.6 (C-12), 46.0 (C-13), 51.0 (C-14), 88.8 (C-17), 118.9 (C-4), 123.8 (C-2), 124.7 (C-7), 128.4 (C-1), 134.5 (C-6), 148.2 (C-3), 125.1 (C-9), 129.5 (C-10), 133.6 (C-5), 148.2 (C-8), 169.4 (17β-O*C*(O)CH_3), 170.7 (3-O*C*(O)CH_3) and 200.0 (C-11).

3-Methoxy-11-oxo-14,17α-ethanoestra-1,3,5(10),6,8-pentaen-17β-ol 81

A solution of the 3,17β-diacetate **80** (756 mg, 1.9 mmol) in methanolic potassium hydroxide (3%, 30 cm^3) was stirred at 25°C for 2 h. Saturated aqueous ammonium chloride (20 cm^3) was added and the mixture was extracted into ethyl acetate (3x). The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to afford a residue (649 mg) which was dissolved in acetone (20 cm^3) and stirred with dimethyl sulfate (0.5 cm^3, 5.3 mmol) and anhydrous potassium carbonate (1 g) for 18 h. Aqueous ammonia (25%, 1 cm^3) was added and the mixture was stirred for 1 h, poured into water (30 cm^3) and extracted with ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to afford a residue (1.2 g). This was chromatographed on silica gel (75 g) with ethyl acetate-toluene (1:4) as eluent to afford the 3-*methyl ether* **81** (353 mg, 56%), m.p. 138-140°C (from acetone-hexane); $[\alpha]_D$ -59° (*c* 0.6) (Found: C, 78.0; H, 7.0%; M^+, 322. $C_{21}H_{22}O_3$ requires C, 78.2; H, 6.9%; *M*, 322); ν_{max}/cm^{-1} 1658 (C=O); δ_H (200 MHz) 0.98 (3H, d, *J* 1.2 Hz, 13β-Me), 1.75 (1H, br. s, D_2O exch., 17β-OH), 2.55 (1H, d, *J* 18 Hz, 12β-H), 2.98 (1H, dd, *J* 18 and 1.2 Hz, 12α-H), 3.92 (3H, s, 3-OMe), 7.12 (1H, d, *J* 2.9 Hz, 4-H), 7.26 (1H, d, *J* 8.3 Hz, 7-H), 7.29 (1H, dd, *J* 9.6 and 2.9 Hz, 2-H), 7.90 (1H, d, *J* 8.3 Hz, 6-H) and 9.30 (1H, d, *J* 9.6 Hz, 1-H); δ_C (50 MHz) 15.7 (13β-Me), 31.3 (C-17^2), 34.6 (C-17^1), 35.8 (C-15), 39.3 (C-16), 45.2 (C-12), 47.9 (C-14), 49.9 (C-13), 55.2 (3-OMe), 83.9 (C-17), 106.6 (C-4), 121.0 (C-2), 124.1 (C-7), 125.2 (C-9), 126.9 (C-10), 128.2 (C-1), 133.6 (C-6), 134.4 (C-5), 146.5 (C-8), 157.2 (C-3) and 200.7 (C-11); δ_H (400MHz, C_6D_6) 0.84 (3H, d, *J* 1.2 Hz, 13β-Me), 2.00 (1H, br. s, 17β-OH), 2.63 (1H, d, *J* 17.6 Hz, 12β-H), 2.88 (1H, dd, *J* 17.6 and 1.2 Hz, 12α-H), 3.39 (3H, s, 3-OMe), 6.95 (1H, d, *J* 2.9 Hz, 4-H), 7.04 (1H, d, *J* 8.3 Hz, 7-H), 7.39 (1H, dd, *J* 9.6 and 2.9 Hz, 2-H), 7.65 (1H, d, *J* 8.3 Hz, 6-H) and 9.93 (1H, d, *J* 9.6 Hz, 1-H); δ_C (100 MHz, C_6D_6) 15.7 (13β-Me), 31.5 (C-17^2), 34.7 (C-17^1), 36.0 (C-15), 39.4 (C-16), 45.8 (C-12), 47.9 (C-14), 50.2 (C-13), 54.7 (3-OMe), 83.6 (C-17), 107.0 (C-4), 121.4 (C-2), 124.4 (C-7), 125.7 (C-9), 126.9 (C-10), 129.1 (C-1), 133.7 (C-6), 135.0 (C-5), 146.8 (C-8), 157.8 (C-3) and 200.4 (C-11).

3-Methoxy-11-oxo-14,17α-ethanoestra-1,3,5(10),8-tetraen-17β-ol 82

To a stirred solution of sodium (1 g, 43.5 mmol) in ammonia (20 cm^3, freshly distilled from sodium) was added the 11-oxo pentaene **81** (137 mg, 0.4 mmol) in dry THF (10 cm^3). After stirring for 15 min at -33°C, t-butyl alcohol (5 cm^3) was added dropwise over a period of 120 min with stirring at -33°C. The mixture was stirred until the blue colour faded (60 min). Water (20 cm^3) was added and the ammonia allowed to evaporate. The resulting mixture was extracted with ethyl acetate, the combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude residue (144 mg). This was chromatographed on silica gel (25 g) with ethyl acetate-toluene (1:4) as eluent to give starting material **81** (31 mg, 23%), followed by the *tetraene* **82** (95 mg, 68%), m.p. 171-173°C (from acetone-hexane); $[\alpha]_D$ -32° (*c* 0.5) (Found: C, 77.6; H, 7.5%; M^+, 324. $C_{21}H_{24}O_3$ requires C, 77.7; H, 7.5%; *M*, 324); ν_{max}/cm^{-1} 1654 (C=O); δ_H (400 MHz) 1.00 (3H, d, *J* 1.2 Hz, 13β-Me), 2.40 (1H, d, *J* 17 Hz, 12β-H), 2.74 (1H, dd, *J* 17 and 1.2 Hz, 12α-H), 3.79 (3H, s, 3-OMe), 6.70 (1H, d, *J* 2.7 Hz, 4-H), 6.78 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.97 (1H, d, *J* 8.6 Hz, 1-H); δ_C (100 MHz) 15.4 (13β-Me), 25.6 (C-7), 28.0 (C-17^2) 29.7 (C-17^1) 34.1 (C-15), 35.5 (C-16), 37.4 (C-6), 44.0 (C-12), 48.8 (C-13), 49.9 (C-14), 55.3 (3-OMe), 83.6 (C-17), 111.0 (C-2), 113.3 (C-4), 124.0 (C-10), 128.3 (C-1), 137.6 (C-5), 156.1 (C-9), 157.3 (C-3), 167.0 (C-8) and 200.3 (C-11).

14,17α-ethano-8α-estra-1,3,5(10)-triene-3,17β-diyl diacetate 83

14,17α-Ethano-8α-estra-1,3,5(10)-triene-3,17β-diol **26** (40 mg, 0.1 mmol) and toluene-*p*-sulfonic acid (10 mg) were dissolved in a mixture of acetic anhydride (2 cm^3) and THF (2 cm^3) and the mixture was stirred for 18h. Saturated aqueous sodium hydrogen carbonate was added and once effervescence ceased the mixture was extracted into ethyl acetate. The combined organic phase was washed [satd. aq. $NaHCO_3$, aq. HCl (1 mol dm^{-3}), water, brine], dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (110 mg) which was chromatographed on silica gel (5 g) with ethyl acetate-toluene (1:19) as eluent to give the 3,17β-*diacetate* **83** (46 mg, 90%), m.p. 187-189°C (from methanol); $[\alpha]_D$ -42° (*c* 0.2) (Found: C, 75.1; H, 8.1%; M^+, 382. $C_{24}H_{30}O_4$ requires C, 75.4; H, 7.9%; *M*, 382); ν_{max}/cm^{-1} 1731 (C=O); δ_H (200 MHz) 1.02 (3H, s, 13β-Me), 2.01 (3H, s, 17β-OC(O)C*H*$_3$),

2.28 (3H, s, 3-OC(O)CH_3), 6.78 (1H, d, *J* 2.3 Hz, 4-H), 6.84 (1H, dd, *J* 8.3 and 2.3 Hz, 2-H) and 7.16 (1H, d, *J* 8.3 Hz, 1-H); δ_C (50 MHz) 15.8 (13β-Me), 20.5 (3-OC(O)*C*H_3), 21.1 (17β-OC(O)*C*H_3), 21.6 (C-7), 28.1 (C-11), 28.5 (C-15), 29.5 (C-12), 30.7 (C-6), 30.9 (C-17^2), 31.6 (C-16), 32.9 (C-17^1), 36.5 (C-8), 38.3 (C-9), 45.0 (C-14), 46.7 (C-13), 90.0 (C-17), 118.7 (C-2), 121.1 (C-4), 130.6 (C-1), 137.8 (C-10), 139.1 (C-5), 148.2 (C-3), 169.8 (17-O*C*(O)CH_3) and 170.9 (3-O*C*(O)CH_3).

6-Oxo-14α,17α-ethano-8α-estra-1,3,5(10)-trien-3,17β-diyl diacetate 84

The 3,17β-diacetate **83** (90 mg, 0.2 mmol) was dissolved in a solution of DMD (0.1 mol dm^{-3} in acetone, 20 cm^3, 2 mmol) and was stirred for 120h at 25°C. The solution was evaporated under reduced pressure to give a crude residue (95 mg) which was filtered through silica gel (10 g) with ethyl acetate-hexane (1:9) to give the 6-*ketone* **84** (44 mg, 47%), m.p. 178-180°C (from methanol); $[\alpha]_D$ +5° (*c* 0.3) (Found: C 73.1; H, 7.3%; M^+, 396. $C_{24}H_{28}O_5$ requires C 72.7; H, 7.1%; *M*, 396); ν_{max}/cm^{-1} 1731 (C=O); δ_H (200 MHz) 1.08 (3H, s, 13β-Me), 2.02 (3H, s, 17β-OC(O)CH_3), 2.30 (3H, s, 3-OC(O)CH_3), 7.25 (1H, dd, *J* 8.5 and 2.5 Hz, 2-H), 7.36 (1H, d, *J* 8.5 Hz, 1-H) and 7.69 (1H, d, *J* 2.5 Hz, 4-H); δ_C (50 MHz) 16.0 (13β-Me), 21.0 (3-OC(O)*C*H_3), 21.5 (17β-OC(O)*C*H_3), 27.2 (C-7), 28.0 (C-11), 29.1 (C-15), 30.3 (C-12), 31.5 (C-17^2), 32.3 (C-16), 36.5 (C-17^1), 36.6 (C-8), 36.9 (C-9), 44.7 (C-14), 47.0 (C-13), 89.6 (C-17), 119.4 (C-2), 127.2 (C-4), 130.8 (C-1), 132.4 (C-10), 145.8 (C-5), 149.2 (C-3), 169.4 (17-O*C*(O)CH_3), 170.7 (3-O*C*(O)CH_3) and 197.4 (C-6).

14-Ethyl-17-oxo-14β-estra-1,3,5(10)-trien-3-yl acetate 86

A solution of 14-ethyl-3-methoxy-14β-estra-1,3,5(10)-trien-17-one **85** [136] (628 mg, 2 mmol) in acetonitrile (15 cm^3) was added to a mixture of chlorotrimethylsilane (0.5 cm^3, 4 mmol) and sodium iodide (600 mg, 4 mmol) in acetonitrile (20 cm^3) and the mixture was refluxed for 96h. Water was added and the resulting mixture was extracted into chloroform. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (700 mg) which was dissolved in a mixture of THF (8 cm^3) and acetic anhydride (5 cm^3). Toluene-*p*-sulfonic acid (200 mg)

was added and the mixture was stirred for 18h at 25°C. Saturated aqueous sodium hydrogen carbonate was added and once effervescence ceased the mixture was extracted into ethyl acetate. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (1 g) which was adsorbed onto silica gel (50 g) and eluted with ethyl acetate-toluene (1:19) to give starting material **85** (26 mg, 4%) followed by the 3-*acetate* **86** (475 mg, 70%), m.p. 132-135°C (from chloroform-methanol); $[\alpha]_D$ +62° (*c* 0.3) (Found: C, 77.3; H, 8.3%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340); ν_{max}/cm^{-1} 1725 (C=O); δ_H (200 MHz) 0.85 (3H, t, *J* 2 x 7.5 Hz, 14^2-H_3), 1.06 (3H, s, 13β-Me), 2.27 (3H, s, 3-OAc), 6.82 (1H, d, *J* 2.6 Hz, 4-H), 6.86 (1H, dd, *J* 8.7 and 2.6 Hz, 2-H) and 7.30 (1H, d, *J* 8.7 Hz, 1-H); δ_C (50 MHz) 10.0 (C-14^2), 15.5 (13β-Me), 21.1 (3-OC(O)*C*H_3), 23.4 (C-7), 25.3 (C-11), 25.5 (C-15), 30.2 (C-14^1), 30.5 (C-6), 33.0 (C-12), 33.7 (C-16), 38.2 (C-9), 41.1 (C-8), 46.4 (C-13), 52.5 (C-14), 118.7 (C-2), 121.3 (C-4), 126.5 (C-1), 138.0 (C-5), 138.1 (C-10), 148.5 (C-3), 169.7 (3-O*C*(O)CH_3) and 222.6 (C-17).

3-Methoxy-15β-phenylthioestra-1,3,5(10)-trien-17-one 88

A solution of 3-methoxyestra-1,3,5(10),15-tetraen-17-one **87** [141] (644 mg, 2.3 mmol) and ethyldiisopropylamine (0.5 cm^3, 2.9 mmol) in thiophenol (5 cm^3, 47.5 mmol) was stirred for 3h in a stoppered flask. The mixture was adsorbed onto silica gel (55 g) and eluted with ethyl acetate-toluene (1:99) to give thiophenol, followed by the 15β-phenylthio 17-ketone **88** (832 mg, 93%), m.p. 112-115°C (from diisopropyl ether); $[\alpha]_D$ +83° (*c* 0.4) (Found: C, 76.2; H, 7.2; S, 8.0%; M^+, 392. $C_{25}H_{28}O_2S$ requires C, 76.5; H, 7.2; S, 8.2%; *M*, 392); ν_{max}/cm^{-1} 1734 (C=O); δ_H (400 MHz, C_6D_6) 1.12 (3H, s, 13β-Me), 1.42 (1H, dd, *J* 11.2 and 7.0, 14α-H), 1.76 (1H, qd, *J* 3 x 11.2 and 2.4 Hz, 8β-H), 2.36 (1H, dd, *J* 19.6 and 8.0 Hz, 16β-H), 2.66 (1H, dd, *J* 19.6 and 1.6 Hz, 16α-H), 3.42 (3H, s, 3-OMe), 3.49 (1H, ddd, *J* 8.0, 7.0 and 1.6 Hz, 15α-H), 6.70 (1H, d, *J* 2.1 Hz, 4-H), 6.81 (1H, dd, *J* 8.6 and 2.1 Hz, 2-H), 7.10 (1H, d, *J* 8.6 Hz, 1-H) and 6.94-7.20 (5H, m, 15β-SC_6H_5); δ_C (100 MHz) 17.0 (13β-Me), 25.5 (C-11), 26.6 (C-7), 29.4 (C-6), 33.1 (C-12), 36.5 (C-8), 43.7 (C-15), 44.4 (C-9), 46.6 (C-16), 47.8 (C-13), 53.7 (C-14), 55.2 (3-OMe), 111.5 (C-2), 113.9 (C-4), 126.1 (C-4'), 126.7 (C-1), 129.2 (C-2' and C-6'), 130.3 (C-3' and C-5'), 131.9 (C-10), 136.8 (C-5), 137.8 (C-1'), 157.7 (C-3) and 218.5 (C-17).

17α-Allyl-3-methoxy-15β-phenylthioestra-1,3,5(10)-trien-17β-ol 89

A solution of the 15β-phenylthio 17-ketone **88** (400 mg, 1.0 mmol) in THF (5 cm^3) was added to a solution of allylmagnesium chloride [prepared from allyl chloride (0.5 cm^3), magnesium (150 mg) and catalytic iodine] in THF (5 cm^3) and the mixture was stirred for 3h. Saturated aqueous ammonium chloride was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product (433 mg) which was recrystallised from methanol to give the 17α-*allyl* 17β-*alcohol* **89** (341 mg, 77%). The mother liquor was adsorbed onto silica gel (4 g) and eluted with ethyl acetate-hexane (1:9) to give further product **89** (26 mg, 6%), m.p. 68-70°C (from methanol); $[\alpha]_D$ +12° (*c* 0.3) (Found: C, 77.2; H, 8.1; S, 7.1%; M^+, 434. $C_{28}H_{34}O_2S$ requires C, 77.4; H, 7.9; S, 7.4%; *M*, 434); ν_{max}/cm^{-1} 3607 (OH); δ_H (400 MHz) 1.23 (3H, s, 13β-Me), 1.62 (1H, s, D_2O exch., 17β-OH), 3.60-3.70 (1H, m, 15α-H), 3.79 (3H, s, 3-OMe), 5.20 (2H, m, 17^3-H_2), 5.88-6.20 (1H, m, 17^2-H), 6.66 (1H, d, *J* 2.1 Hz, 4-H), 6.74 (1H, dd, *J* 8.6 and 2.1 Hz, 2-H) and 7.18-7.40 (6H, m, 1-H and 15β-SC_6H_5); δ_C (100 MHz) 17.0 (13β-Me), 25.7 (C-11), 27.9 (C-7), 29.5 (C-6), 32.5 (C-12), 37.2 (C-8), 41.0 (C-17^1), 44.2 (C-9), 45.1 (C-15), 46.6 (C-13), 47.5 (C-16), 52.7 (C-14), 55.2 (3-OMe), 82.5 (C-17), 111.4 (C-2), 113.9 (C-4), 119.4 (C-17^3), 126.0 (C-4'), 126.1 (C-1), 128.9 (C-2' and C-6'), 129.8 (C-3' and C-5'), 132.4 (C-10), 134.4 (C-17^2), 138.0 (C-5), 138.1 (C-1') and 157.6 (C-3).

Attempted cyclisation of 17α-allyl 15β-phenylthio 17β-alcohol 89

a) To a solution of the 17α-allyl 15β-phenylthio 17β-alcohol **89** (97 mg, 0.2 mmol) and AIBN (10 mg) in dry, deoxygenated toluene (10 cm^3) was added tributylstannane (1 cm^3) and the mixture was refluxed for 3 h. The solvent was removed under reduced pressure and the residue (1.3 g) was chromatographed on silica gel (30 g) with ethyl acetate-toluene (1:19) as eluent to give starting material **89** (19 mg, 20%) followed by an inseparable mixture of 17α-allyl-3-methoxyestra-1,3,5(10)-trien-17β-ol **90** and 17α-allyl-3-methoxyestra-1,3,5(10),14-tetraen-17β-ol **91** (37 mg), *m/z* 324 and 326, δ_H (200 MHz) (**90**, *ca.* 70%) 0.93 (3H, s, 3-OMe), 3.78 (3H, s, 3-OMe), 5.20 (2H, m, 17^3-H_2), 5.85-6.15

(1H, m, 17^2-H), 6.64-6.74 (2H, m, 2- and 4-H) and 7.24 (1H, br. d, *J* 9 Hz, 1-H); δ_H (200 MHz) (**91**, *ca.* 30%) 0.96 (3H, s, 13β-Me), 3.78 (3H, s, 3-OMe), 5.20 (2H, m, 17^3-H_2), 5.68 (1H, dd, *J* 6.0 and 3.2 Hz, 15-H), 5.85-6.15 (1H, m, 17^2-H), 6.64-6.74 (2H, m, 2- and 4-H) and 7.24 (1H, br. d, *J* 9 Hz, 1-H).

b) A solution of the 17α-allyl 15β-phenylthio 17β-alcohol **89** (54 mg, 0.1 mmol) in THF (10 cm^3) was added to a solution of sodium (150 mg, 6.5 mmol) in freshly distilled ammonia (10 cm^3) at -33°C and the mixture was stirred at -33°C for 2h. The ammonia was allowed to evaporate, water was added and the resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (18 mg) which was chromatographed on silica gel (3 g) with ethyl acetate-hexane (1:9) as eluent to give 17α-allyl-3-methoxyestra-1,3,5(10)-trien-17β-ol **90** (11 mg, 28%), m.p. 90-91°C (from diethyl ether-hexane); $[\alpha]_D$ +62° (*c* 0.2) (lit., [146] 91-91.5°C, $[\alpha]_D$ +57.4°) (Found: M^+, 326. $C_{22}H_{30}O_2$ requires *M*, 326); δ_H (200 MHz) 0.93 (3H, s, 13β-Me), 2.84 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 5.20 (2H, m, 17^3-H_2), 5.90-6.15 (1H, m, 17^2-H), 6.64 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.7 Hz, 2-H) and 7.22 (1H, d, *J* 8.6 Hz, 1-H).

17α-Allyl-3-methoxyestra-1,3,5(10),15-tetraen-17β-ol 92

A solution of 3-methoxyestra-1,3,5(10),15-tetraen-17-one **87** (2.0 g, 7.1 mmol) in THF (40 cm^3) was added to a solution of allylmagnesium bromide [prepared from allyl bromide (6 cm^3, 69.3 mmol), magnesium (1.6 g, 66.7 mmol) and catalytic iodine] in diethyl ether (20 cm^3). The resulting solution was refluxed for 90 min. Saturated aqueous ammonium chloride was added to the cooled reaction mixture, and once effervescence had ceased the mixture was extracted into ethyl acetate. The combined organic extracts were washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to afford the product **92** (2.24 g), a portion of which was chromatographed and recrystallised for characterisation purposes: m.p. 112-113°C (from methanol); $[\alpha]_D$ -76° (*c* 0.7) [lit., [157] 106-108°C (from acetone-hexane); $[\alpha]_D$ -76.8°] (Found: C, 81.5; H, 8.7%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324); ν_{max}/cm^{-1} 3607 (OH); δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 1.85 (1H, s, D_2O exch., 17β-OH), 2.90 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 5.20 (2H, m, $W_{½}$ 18

Hz, 17^3-H_2), 5.67 (1H, dd, *J* 6.0 and 3.2 Hz, 15-H), 5.82-6.00 (1H, m, 17^2-H), 5.99 (1H, dd, *J* 6.0 and 1.6 Hz, 16-H), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.21 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 15.0 (13β-Me), 26.0 (C-11), 27.8 (C-7), 29.6 (C-6), 30.6 (C-12), 36.7 (C-17^1), 37.9 (C-8), 44.5 (C-9), 51.4 (C-13), 55.2 (3-OMe), 56.3 (C-14), 86.0 (C-17), 111.4 (C-2), 113.9 (C-4), 118.6 (C-17^3), 126.0 (C-1), 130.8 (C-15), 132.5 (C-10), 134.9 (C-16), 137.6 (C-17^2), 137.8 (C-5) and 157.5 (C-3).

15α-Allyl-3-methoxyestra-1,3,5(10)-trien-17-one 93

A solution of the 17α-allyl 17β-alcohol **92** (2.2 g, 6.9 mmol) in dry 1,4-dioxan (25 cm^3) was added to a suspension of potassium hydride [4g of 35% suspension in mineral oil, 35 mmol; pre-washed with hexane (3 x 10 cm^3) and treated with a solution of iodine (440 mg, 3.5 mmol) [190] in dry 1,4-dioxan (2 cm^3)] and 18-crown-6 (50 mg, 0.2 mmol) in dry 1,4-dioxan (15 cm^3) and the resulting mixture was refluxed for 1h. To the cooled (0°C) suspension was added saturated aqueous ammonium chloride. After the effervescence ceased, the mixture was extracted with ethyl acetate. The combined organic phase was washed (satd. aq. $Na_2S_2O_3$, water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (2.63 g) which was flash chromatographed on silica gel (180 g) with toluene affording the 15α-allyl 17-ketone **93** (1.93 g, 86%) followed by a mixture of products (320 mg) which was rechromatographed on silica gel (30 g) with ethyl acetate-hexane (1:4) as eluent affording further 15α-allyl 17-ketone **93** (171 mg, 8%), m.p. 91-93°C (from ethanol); $[\alpha]_D$ +251° (*c* 0.5) [lit., [157] 79-80°C (from acetone-hexane); $[\alpha]_D$ +211.4°] (Found: C, 81.4; H, 8.7%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324); ν_{max}/cm^{-1} 1728 (C=O); δ_H (400 MHz) 0.97 (3H, s, 13β-Me), 1.33 (1H, t, *J* 2 x 10.8 Hz, 14α-H), 1.65 (1H, dd, *J* 19.4 and 7.8 Hz, 16β-H), 1.80 (1H, qd, *J* 10.8 and 2.7 Hz, 8β-H), 2.02 (1H, td, *J* 11.0 and 4.2 Hz, 15^1-H_1), 2.71 (1H, dd, *J* 19.4 and 8.7 Hz, 16α-H), 2.88 (2H, m, 6-H_2), 3.77 (3H, s, 3-OMe), 4.95 (2H, m $W_{½}$ 26 Hz, 15^3-H_2), 5.52-5.63 (1H, m, 15^2-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.20 (1H, d, *J* 8.5 Hz, 1-H); δ_C (100 MHz) 15.7 (13β-Me), 26.5 (C-11), 27.9 (C-7), 30.0 (C-6), 31.6 (C-12), 35.5 (C-15), 39.7 (C-8), 40.4 (C-15^1), 42.6 (C-16), 44.2 (C-9), 50.4 (C-13), 54.1 (C-14), 55.2 (3-OMe), 111.8 (C-2), 113.6 (C-4), 116.6 (C-15^3), 126.8 (C-1), 131.8 (C-10), 136.3 (C-15^2), 137.3 (C-5), 157.6 (C-3) and 219.5 (C-17).

17α-Methallyl-3-methoxyestra-1,3,5(10),15-tetraen-17β-ol 94

A solution of 3-methoxyestra-1,3,5(10),15-tetraen-17-one **87** (100 mg, 0.4 mmol) in THF (5 cm^3) was added to a solution of methallylmagnesium chloride [prepared from methallyl chloride (0.4 cm^3, 3.5 mmol), magnesium (85 mg, 3.5 mmol) and catalytic iodine] in diethyl ether (2 cm^3) and the resulting mixture was stirred for 30 min at 25°C. Saturated aqueous ammonium chloride was added to the cooled reaction mixture, and the resulting mixture was extracted into ethyl acetate. The combined organic extracts were washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude residue (103 mg) which was adsorbed onto silica gel (10 g) and eluted with ethyl acetate-hexane (1:9) affording the 17α-*methallyl* 17β-*alcohol* **94** (85 mg, 72%), m.p. 70-73°C (from methanol); $[\alpha]_D$ -68° (*c* 0.3) (Found: C, 81.6; H, 9.1%; M^+, 338. $C_{23}H_{30}O_2$ requires C, 81.6; H, 8.9%; *M*, 338); ν_{max}/cm^{-1} 3605 (OH); δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 1.83 (3H, s, 17^2-Me), 2.10 (1H, s, D_2O exch., 17β-OH), 2.95 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 4.90 (1H, br. s, 17^3-H), 4.96 (1H, br. s, 17^3-H), 5.66 (1H, dd, *J* 6.0 and 3.1 Hz, 15-H), 5.95 (1H, dd, *J* 6.0 and 1.6 Hz, 16-H), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.20 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 15.0 (13β-Me), 25.0 (17^2-Me), 26.0 (C-11), 27.8 (C-7), 29.6 (C-6), 30.4 (C-12), 36.7 (C-17^1), 40.9 (C-8), 44.4 (C-9), 52.0 (C-13), 55.2 (3-OMe), 56.0 (C-14), 85.6 (C-17), 111.4 (C-2), 113.9 (C-4), 114.8 (C-17^3), 126.0 (C-1), 130.1 (C-15), 132.6 (C-10), 137.8 (C-5), 138.0 (C-16), 143.7 (C-17^2) and 157.5 (C-3).

15α-Methallyl-3-methoxyestra-1,3,5(10)-trien-17-one 95

The 17α-methallyl 17β-alcohol **94** (78 mg, 0.2 mmol) in dry 1,4-dioxan (5 cm^3) was added to a suspension of potassium hydride [300 mg of 35% suspension in mineral oil, 2.5 mmol; washed with hexane (3 x 1 cm^3) and treated with iodine (64 mg, 0.25 mmol in dry 1,4-dioxan (1 cm^3)] and 18-crown-6 (10 mg, 0.1 mmol) in dry 1,4-dioxan (5 cm^3) and the mixture was refluxed for 30 min. To the cooled (0°C) suspension was added saturated aqueous ammonium chloride and once effervescence ceased, the mixture was extracted with ethyl acetate. The combined organic phase was washed (satd. aq. $Na_2S_2O_3$, water,

brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (112 mg) which was chromatographed on silica gel (5 g) with ethyl acetate-toluene (1:99) to give the 15α-*methallyl* 17-*ketone* **95** (58 mg, 75%), m.p. 129-130°C (from chloroform-methanol); $[\alpha]_D$ +191° (*c* 0.2) (Found: C, 81.2; H, 9.1%; M^+, 338. $C_{23}H_{30}O_2$ requires C, 81.6; H, 8.9%; *M*, 338); ν_{max}/cm^{-1} 1727 (C=O); δ_H (200 MHz) 0.99 (3H, s, 13β-Me), 1.30 (1H, t, *J* 2 x 10.6 Hz, 14α-H), 1.74 (3H, s, 15^2-Me), 2.88 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 4.69 (1H, br. s, 15^3-H), 4.75 (1H, br. s, 15^3-H), 6.62 (1H, d, *J* 2.8 Hz, 4-H), 6.72 (1H, dd, *J* 8.6 and 2.8 Hz, 2-H) and 7.21 (1H, d, *J* 8.6 Hz, 1-H); δ_C (50 MHz) 15.8 (13β-Me), 22.5 (C-15^2Me), 26.6 (C-11), 27.9 (C-7), 30.0 (C-6), 31.6 (C-12), 33.7 (C-15), 39.7 (C-8), 42.8 (C-15^1), 44.3 (C-9), 45.5 (C-16), 50.5 (C-13), 55.2 (3-OMe), 55.4 (C-14), 111.6 (C-15^3), 111.8 (C-2), 113.5 (C-4), 126.8 (C-1), 131.8 (C-10), 137.3 (C-5), 144.1 (C-15^2), 157.6 (C-3) and 219.7 (C-17).

15β-Allyl-3-methoxyestra-1,3,5(10)-trien-17-one 96

a) To a vigorously stirred solution of 3-methoxyestra-1,3,5(10),15-tetraen-17-one **87** (50 mg, 0.2 mmol) in dry dichloromethane (2 cm^3) at -78°C was added titanium tetrachloride (0.1 cm^3, 0.9 mmol) to give a brick-red solution which was stirred for 5 min. Allyltrimethylsilane (0.2 cm^3, 1.0 mmol) in dry dichloromethane (1 cm^3) was added over 15 min and the resultant purple solution was stirred for 1h at -78°C. Ice-water was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (51 mg) which was adsorbed onto silica gel (5 g) and eluted with ethyl acetate-hexane (1:9) to give 15β-allyl-3-methoxyestra-1,3,5(10)-trien-17-one **96** (19 mg, 32%), m.p. 122-123 °C (from diisopropyl ether); $[\alpha]_D$ +77° (*c* 0.9) [lit., [157] 103-104°C (from hexane); $[\alpha]_D$ +81°] (Found: C, 81.1; H, 8.8%; M^+, 324. $C_{22}H_{28}O_2$ requires C, 81.4; H, 8.7%; *M*, 324); ν_{max}/cm^{-1} 1725 (C=O); δ_H (200 MHz) 1.05 (3H, s, 13β-Me), 2.90-3.00 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 5.04 (2H, m, 15^3-H_2), 5.65-5.85 (1H, m, 15^2-H), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.20 (1H, d, *J* 8.5 Hz, 1-H).

b) Ethylaluminium dichloride (1.8 mol dm^{-3} in toluene, 0.5 cm^3, 0.9 mmol) was added to a solution of the Δ^{15} 17-ketone **87** (50 mg, 0.2 mmol) in dichloromethane (2 cm^3) at -78°C

and the mixture was allowed to stir for 5 min. A solution of allyltrimethylsilane (0.2 cm^3, 1.0 mmol) in dichloromethane (1 cm^3) was added dropwise over 15 min and the resultant solution was stirred for 3h at -78°C and 1 h at 0°C. Work-up as in (**a**) afforded a residue (63 mg) which was adsorbed onto silica gel (5 g) and eluted with ethyl acetate-hexane (1:9) to give the 15β-allyl 17-ketone **96** (32 mg, 55%), identical to that described previously.

c) Tin tetrachloride (1 mol dm^{-3} in dichloromethane, 0.9 cm^3, 0.9 mmol) was added to a solution of the Δ^{15} 17-ketone **87** (50 mg, 0.2 mmol) in dichloromethane (1 cm^3) at -78°C and the mixture was allowed to stir for 5 min. A solution of allyltrimethylsilane (0.2 cm^3, 1.0 mmol) in dichloromethane (1 cm^3) was added dropwise over 15 min and the resultant solution was stirred for 8h at -78°C and 25°C for 18h. Work-up as in (**a**) afforded a residue (85 mg) which was adsorbed onto silica gel (5 g) and eluted with ethyl acetate-hexane (1:9) to give the 15β-allyl 17-ketone **96** (33 mg, 55%), identical to that described previously.

d) Copper(I) iodide (200 mg, 1.05 mmol) and dry lithium chloride (450 mg, 1.05 mmol) were placed in a 25 cm^3 flask which was evacuated and purged with nitrogen. This process was repeated three times, then THF(3 cm^3) was added and the mixture was stirred for 5 min to give a homogenous yellow solution which was cooled to -78°C. A solution of allyl lithium [prepared from allyltributyltin (0.3 cm^3, 1 mmol) and methyl lithium (1.5 mol dm^{-3} in diethyl ether, 0.7 cm^3, 1 mmol) in THF (1 cm^3) stirred at -78°C for 15 min] was then added in one portion to give a tan solution. To this solution was added chlorotrimethylsilane (0.1 cm^3, 1.2 mmol) followed by the Δ^{15} 17-ketone **87** (50 mg, 0.2 mmol) in THF (2 cm^3) and the mixture was stirred for 4h at -78°C. Saturated aqueous ammonium chloride (10 cm^3) was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (80 mg) which was adsorbed onto silica gel (15 g) and eluted with ethyl acetate-hexane (1:9) to give tin residues followed by 3-methoxyestra-1,3,5(10),14-tetraen-17-one **97** (11 mg, 22%), m.p. 100-103 °C (from methanol) (lit., [141] 103-104°C); δ_H (200 MHz) 1.16 (3H, s, 13β-Me), 3.79 (3H, s, 3-OMe), 5.61 (1H, m, 15-H), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.20 (1H, d, *J* 8.5 Hz, 1-H). Further elution with the same solvent afforded starting material **87** (13 mg, 26%).

e) Copper(I) cyanide (90 mg, 1 mmol) was dried under vacuum and then suspended in THF (0.9 cm^3) and cooled to -78°C. Methyl lithium (1.5 mol dm^{-3} in diethyl ether, 1 cm^3, 1.5 mmol) was added and the mixture allowed to warm to 0°C, during which time the suspension dissolved to give a pale yellow solution. Allyltributyltin (0.6 cm^3, 1.8 mmol) was added and the mixture was stirred at 0°C for 30 min and then cooled to -78°C. To the resulting orange-yellow solution was added the Δ^{15} 17-ketone **87** (50 mg, 0.2 mmol) in THF (2 cm^3) and the initially formed deep orange colour rapidly faded to the original orange-yellow colour. The mixture was stirred for a further 30 min at -78°C, then a mixture of saturated aqueous ammonium chloride and aqueous ammonia (10%) (1:1) was added and the mixture allowed to warm up to 25°C. The resultant solution was extracted into diethyl ether, the combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (100 mg) which was combined with a similar residue from an identical experiment and the mixture was adsorbed onto silica gel (20 g) and eluted with ethyl acetate-toluene (1:99) to give tin residues followed by an inseparable mixture of 15α-allyl-17-ketone **93** and 15β-allyl-17-ketone **96** (40 mg, 33%) (*ca.* 1:3). The composition of the mixture was estimated from the ^1H NMR spectrum using the signals for the 13β-Me: **93**, δ_H (200 MHz) 0.97 (3H, s, 13β-Me) and **96**, δ_H (200 MHz) 1.05 (3H, s, 13β-Me). Further elution with the same solvent afforded the 17α-allyl 17β-alcohol **92** (79 mg, 67%), m.p. 108-111°C (from methanol).

f) Copper(I) cyanide (90 mg, 1 mmol) was dried under vacuum and then suspended in THF (0.9 cm^3) and cooled to -78°C. Methyl lithium (1.5 mol dm^{-3} in diethyl ether, 1 cm^3, 1.5 mmol) was added and the mixture allowed to warm to 0°C, during which time the suspension dissolved to give a pale yellow solution. A solution of allyltriphenyltin (366 mg, 1.8 mmol) in THF (1.5 cm^3) was added and the mixture was stirred at 0°C for 30 min and then cooled to -78°C. To the resulting orange-yellow solution was added the Δ^{15} 17-ketone **87** (50 mg, 0.2 mmol) in THF (2 cm^3) and the initially formed deep orange colour rapidly faded to the original orange-yellow colour. The mixture was stirred for a further 30 min at -78°C, then a mixture of saturated aqueous ammonium chloride and aqueous ammonia (10%) (1:1) was added and the mixture allowed to warm up to 25°C. The resultant solution was extracted into diethyl ether, the combined organic phase was

washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (241 mg) which was adsorbed onto silica gel (10 g) and eluted with ethyl acetate-hexane (1:9) to give 3-*methoxy*-15β-*phenylestra*-1,3,5(10)-*trien*-17-*one* **98** (50 mg, 77%), m.p. 123-124°C (from diisopropyl ether); $[\alpha]_D$ +21° (*c* 0.4) (Found: C 83.2; H, 8.0%; M^+, 360. $C_{25}H_{28}O_2$ requires C, 83.3; H, 7.8%; *M*, 360); ν_{max}/cm^{-1} 1726 (C=O); δ_H (200 MHz) 0.88 (3H, s, 13β-Me), 3.78 (3H, s, 3-OMe), 3.90 (1H, m, 15α-H), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.17-7.38 (6H, m, 1-H and 15β-C_6H_5); δ_C (50 MHz) 17.6 (13β-Me), 25.6 (C-11), 27.7 (C-7), 29.4 (C-6), 34.2 (C-12), 37.1 (C-8), 38.6 (C-15), 44.9 (C-9), 45.0 (C-16), 47.3 (C-13), 55.0 (C-14), 55.2 (3-OMe), 111.5 (C-2), 113.8 (C-4), 126.0 (C-4'), 126.1 (C-1), 128.3 (C-2' and C-6'), 128.4 (C-3' and C-5'), 132.3 (C-10), 137.7 (C-5), 142.8 (C-1'), 157.7 (C-3) and 221.0 (C-17).

15α-Acetonyl-3-methoxyestra-1,3,5(10)-trien-17-one 99

A suspension of palladium(II) chloride (6 mg, 0.03 mmol) and copper(I) chloride (31 mg, 0.3 mmol) in a mixture of dimethylformamide (DMF) (2 cm^3) and water (0.2 cm^3) was stirred at 25°C under an oxygen atmosphere for 3h. To this suspension was added 15α-allyl-3-methoxyestra-1,3,5(10)-trien-17-one **93** (100 mg, 0.3 mmol) in a mixture of DMF (5 cm^3) and water (0.5 cm^3) and the mixture was stirred at 25°C under an oxygen atmosphere for 24h, poured into cold hydrochloric acid (3 mol dm^{-3}, 20 cm^3) and the resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (satd. aq. $NaHCO_3$, water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (97 mg) which was adsorbed onto silica gel (10 g) and eluted with ethyl acetate-toluene (1:19) to give starting material **93** (5 mg, 4%) followed by the *diketone* **99** (91 mg, 87%), m.p. 144-147°C (from chloroform-methanol); $[\alpha]_D$ +221° (*c* 0.3) (Found: C, 77.3; H, 8.3%; M^+, 340. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.3%; *M*, 340); ν_{max}/cm^{-1} 1728 (C=O); δ_H (200 MHz) 0.99 (3H, s, 13β-Me), 1.33 (1H, t, *J* 2 x 10.7 Hz, 14α-H), 2.17 (3H, s, 15^3-Me), 3.77 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H) and 7.20 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 15.5 (13β-Me), 26.5 (C-11), 27.8 (C-7), 29.8 (C-6), 30.4 (C-15^3), 31.0 (C-15^1), 31.5 (C-12), 39.5 (C-8), 43.9 (C-16), 44.1 (C-9), 49.8 (C-13), 50.9 (C-15), 54.1 (C-14), 55.2 (3-OMe), 111.8 (C-2),

113.5 (C-4), 126.7 (C-1), 131.5 (C-10), 137.0 (C-5), 157.6 (C-3), 207.2 (C-15[2]) and 219.0 (C-17).

Attempted aldol closure of the diketone 99

a) *n*-Butyllithium (1.6 mol dm^{-3} in hexanes, 0.15 cm^3; 0.2 mmol) was added to a cooled (-10°C, acetone-dry ice) solution of hexamethyldisilazane (0.2 cm^3, 0.9 mmol) in THF (0.5 cm^3) and the mixture was stirred for 45 min at -10°C and then cooled to -78°C. To this solution was added the diketone **99** (44 mg, 0.1 mmol) in THF (1 cm^3) and the mixture was stirred for 3h at -78°C. Saturated aqueous ammonium chloride was then added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give starting material **99** (43 mg, 98%).

b) *n*-Butyllithium (1.6 mol dm^{-3} in hexanes, 0.15 cm^3; 0.2 mmol) was added to a cooled (-10°C, acetone-dry ice) solution of diisopropylamine (0.2 cm^3, 2.7 mmol) in THF (3 cm^3) and the mixture was stirred for 45 min at -10°C and then cooled to -78°C. To this solution was added the diketone **99** (66 mg, 0.2 mmol) in THF (2 cm^3) and the mixture was stirred for 1h at -78°C. Work-up, as in (**a**) afforded starting material **99** (44 mg).

c) A solution of the diketone **99** (15 mg, 0.05 mmol) in 1,4-dioxane (1 cm^3) was added to a suspension of sodium hydride [10 mg of a 50% suspension in mineral oil, 0.2 mmol; washed with hexane (3 x 2 cm^3)] in 1,4-dioxane (1 cm^3) at 25°C and the mixture was stirred for 5h at 25°C. Work-up as in (**a**) afforded starting material **99** (12 mg).

d) The diketone **99** (14 mg, 0.05 mmol) was refluxed in a solution of sodium methoxide (0.2 mol dm^{-3}, 5 cm^3) for 6h. The cooled solution was subjected to a work-up as in (**a**) to give starting material **99** (12 mg).

e) The diketone **99** (5 mg, 0.01 mmol) was stirred in a methanolic potassium hydroxide solution (1%; 1 cm^3) for 48h. Work-up as in (**a**) afforded starting material **99** (3 mg)

Attempted intramolecular reductive coupling of the diketone 99

A solution of the diketone **99** (10 mg, 0.1 mmol) in THF (1 cm^3) was added to a solution of samarium(II) iodide [prepared from samarium (100 mg) and diiodoethane (180 mg)] in THF (2 cm^3), and the mixture was refluxed for 3h. Saturated aqueous ammonium chloride was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (satd. aq. $Na_2S_2O_3$, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue, identified as a complex mixture of 15^2,17-diols **100** (8 mg) (ν_{max}/cm^{-1} 3602, 3400 br.; *m/z* 344) which was suspended in dichloromethane (2 cm^3). Dess-Martin periodinane [72] (100 mg) was added and the resulting mixture was stirred for 1h. Diethyl ether (5 cm^3) was added, and the mixture was poured into saturated aqueous sodium hydrogen carbonate solution (5 cm^3) containing sodium thiosulfate (500 mg). The resulting mixture was extracted into diethyl ether. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give the diketone **99** (5 mg, 50%), m.p. 142-145°C (from chloroform-methanol).

15α-Allyl-3-methoxyestra-1,3,5(10)-trien-17β-ol 103

LAH (250 mg, 6.6 mmol) was added to a solution of 15α-allyl-3-methoxyestra-1,3,5(10)-trien-17-one **93** (442 mg, 1.4 mmol) in THF (10 cm^3) and the solution was stirred for 15 min at 25°C. Ethyl acetate (10 cm^3) was added and once effervescence ceased the mixture was poured into saturated aqueous sodium hydrogen carbonate (10 cm^3) and the resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give the 17β-*alcohol* **103** (445 mg, 99%) m.p. 112-113°C (from methanol); $[\alpha]_D$ +153° (*c* 0.8) (Found: C, 80.6; H, 9.4%; M^+, 326. $C_{22}H_{30}O_2$ requires C, 80.9; H, 9.3%; *M*, 326); ν_{max}/cm^{-1} 3607 (OH); δ_H (200 MHz) 0.82 (3H, s, 13β-Me), 1.02 (1H, t, *J* 2 x 8.8 Hz, 14α-H), 1.61 (1H, s, D_2O exch., 17β-OH), 2.85 (2H, m, 6-H_2), 3.68 (1H, t, *J* 2 x 9 Hz, 17α-H), 3.78 (3H, s, 3-OMe), 5.05 (2H, m $W_{½}$ 17 Hz, 15^3-H_2), 5.71-5.84 (1H, m, 15^2-H), 6.61 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.20 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 12.1 (13β-Me), 26.9 (C-11), 28.0 (C-7), 30.1 (C-6), 36.0 (C-12), 36.6 (C-15), 37.8 (C-15^1), 39.6 (C-8), 41.5 (C-16), 44.3 (C-9), 45.1 (C-13), 54.5 (C-14), 55.2 (3-OMe), 80.0 (C-17), 111.7

(C-2), 113.5 (C-4), 115.6 (C-15^3), 126.7 (C-1), 132.4 (C-10), 137.5 (C-15^2), 137.6 (C-5) and 157.4 (C-3).

15α-(3-Hydroxypropyl)-3-methoxyestra-1,3,5(10)-trien-17β-ol 101

a) Borane-dimethyl sulfide (10 mol dm^{-3}, 0.5 cm^3, 5 mmol) was added to a solution of 15α-allyl-3-methoxyestra-1,3,5(10)-trien-17-one **93** (170 mg, 0.5 mmol) in THF (5 cm^3) and the mixture was stirred for 3h. The mixture was then cooled to 0°C, hydrogen peroxide (100 vol, 10 cm^3) and aqueous sodium hydroxide (4 mol dm^{-3}, 5 cm^3) were added and the mixture was stirred for 18h. Water (10 cm^3) was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (161 mg) which was flash chromatographed on silica gel (20 g) with ethyl acetate-toluene (1:9) to give an unidentified product (17 mg). Further elution with ethyl acetate-toluene (3:2) afforded an inseparable mixture of the 15α-hydroxypropyl 17β-alcohol **101** and the 15α-hydroxypropyl 17α-alcohol **102** (70 mg, 39%) in approximately a 1:1 ratio (from ^{1}H NMR). The presence of the 15α-hydroxypropyl 17α-alcohol **102** was evident from the duplication of certain signals in the ^{1}H NMR spectrum, *viz.* δ_H 0.75 (3H, s, 13β-Me) and 7.21 (1H, d, *J* 8.8 Hz, 1-H).

b) Borane-dimethyl sulfide (10 mol dm^{-3}, 0.9 cm^3, 9 mmol) was added to a cooled (0°C) solution of cyclohexene (0.3 cm^3, 3.1 mmol) in dry diethyl ether (10 cm^3) and the mixture was stirred at 0°C for 3h, during which, white dicyclohexylborane precipitated out of solution. To this suspension was added the 15α-allyl 17-ketone **93** (90 mg, 0.3 mmol) in THF (3 cm^3) and the mixture was stirred at 25°C for 18h. Water (6 cm^3) and sodium perborate tetrahydrate (1 g) were added and the mixture was stirred vigorously for 3h and then was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (200 mg) which was flash chromatographed on silica gel (20 g) with ethyl acetate-toluene (4:1) to give the 15α-*hydroxypropyl* 17β-*alcohol* **101** (56 mg, 59%), m.p. 168-171°C (from ethyl acetate); $[\alpha]_D$ +152° (*c* 0.6 in THF) (Found: C, 76.6; H, 9.5%; M$^+$, 344. $C_{22}H_{32}O_3$ requires C, 76.7; H, 9.4%; *M*, 344); ν_{max}/cm^{-1} 3465 br. (OH); δ_H (200 MHz) 0.81 (3H, s, 13β-Me),

1.52-1.56 (2H, m, D_2O exch., 15^3- and 17β-OH), 2.80-2.90 (2H, m, 6-H_2), 3.61-3.70 (3H, m, 15^3-H_2 and 17α-H), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.5 Hz, 4-H), 6.71 (1H, dd, *J* 8.8 and 2.5 Hz, 2-H) and 7.20 (1H, d, *J* 8.8 Hz, 1-H).

c) Reaction conditions identical to those described in (**a**) were applied to the 15α-allyl 17β-alcohol **103** (170 mg, 0.5 mmol). Flash chromatography on silica gel (50 g) with ethyl acetate-toluene (1:4) afforded an unidentified product (5 mg). Further elution with ethyl acetate-toluene (2:3) afforded the 15α-hydroxypropyl 17β-alcohol **101** (101 mg, 57%), identical to that described previously.

15α-Formylethyl-3-methoxyestra-1,3,5(10)-trien-17-one 104

To a stirred suspension of the 15α-hydroxypropyl 17β-alcohol **101** (101 mg, 0.3 mmol) in dry chloroform (5 cm^3) was added Dess-Martin periodinane [72] (600 mg, 2.3 mmol) and the mixture was stirred for 2h. Diethyl ether was added and the mixture was poured into saturated aqueous sodium hydrogen carbonate solution (20 cm^3) with sodium thiosulfate (2 g) dissolved in it. The mixture was stirred for 5 min and extracted with diethyl ether. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give the formylethyl ketone **104** (97 mg, 98%), as an oil, ν_{max}/cm^{-1} 1727 (C=O); *m/z* 340; δ_H (200 MHz) 0.95 (3H, s, 13β-Me), 2.80-2.90 (2H, m, 6-H_2), 3.76 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.8 and 2.8 Hz, 2-H), 7.20 (1H, d, *J* 8.8 Hz, 1-H) and 9.79 (1H, br. s, 15^3-H).

Attempted intramolecular reductive coupling of the 15α-formylethyl 17-ketone 104

a) A solution of the formylethyl ketone **104** (139 mg, 0.4 mmol) in THF (5 cm^3) was added to a solution of samarium(II) iodide [prepared from samarium (700 mg, 4.7 mmol) and diiodoethane (1.3 g, 4.8 mmol)] in THF (10 cm^3) at 0°C and the mixture was stirred for 30 min at 0°C and for 4h at 25°C. Saturated aqueous ammonium chloride was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (satd. aq. $Na_2S_2O_3$, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (116 mg) which was adsorbed onto silica gel (14 g) and eluted with ethyl acetate-

toluene (7:3) to give a complex mixture of products (31 mg), followed by the 15α-hydroxypropyl 17β-alcohol **101** (35 mg, 25%) identical to that described previously.

b) A solution of the formylethyl ketone **104** (97 mg, 0.3 mmol) in THF (4 cm^3) was added to a solution of samarium(II) iodide [prepared from samarium (350 mg, 2.3 mmol) and diiodoethane (660 mg, 2.3 mmol)] in THF (5 cm^3) and the mixture was stirred for 72 h at 25°C, and then at reflux for 4h. Work-up as in (**a**) gave a residue (69 mg) which was adsorbed onto silica gel (5 g) and eluted with ethyl acetate-toluene (2:3) to give a complex mixture of products (35 mg), followed by 15α-(3-hydroxypropyl)-3-methoxyestra-1,3,5(10)-trien-17-one **105** (5 mg, 5%), as an oil, (Found: M^+, 342. $C_{22}H_{30}O_3$ requires *M*, 342); ν_{max}/cm^{-1} 3615 (OH) and 1727 (C=O); δ_H (400 MHz) 0.96 (3H, s, 13β-Me), 1.58 (1H, m, D_2O exch., 15^3-OH), 1.78 (1H, dd, *J* 19.1 and 8.0 Hz, 16β-H), 2.79 (1H, dd, *J* 19.1 and 8.7 Hz, 16α-H), 2.85 (2H, m, 6-H_2), 3.64 (2H, t, *J* 2 x 6.3 Hz, 15^3-H_2), 3.77 (3H, s, 3-OMe), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.71 (1H, dd, *J* 8.7 and 2.8 Hz, 2-H) and 7.20 (1H, d, *J* 8.7 Hz, 1-H).

Attempted ketyl-olefin coupling of the 15α-allyl-17-ketone 93

A solution of 15α-allyl-3-methoxyestra-1,3,5(10)-trien-17-one **93** (100 mg, 0.3 mmol) in THF (2 cm^3) was added to a solution of samarium(II) iodide [prepared from samarium (350 mg, 2.3 mmol) and diiodoethane (660 mg, 2.3 mmol)] in THF (5 cm^3) and the mixture was stirred for 1h at 25°C. t-Butyl alcohol (80 mg, 1.1 mmol) in THF (1 cm^3) was added and the mixture was refluxed for 40h (further t-butyl alcohol was added after 6 and 24h). Saturated aqueous ammonium chloride was added and the mixture was extracted into ethyl acetate. The combined organic phase was washed (satd. aq. $Na_2S_2O_3$, water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (99 mg) which was adsorbed onto silica gel (12 g) and eluted with ethyl acetate-toluene (1:19) to give starting material **93** (15 mg, 15%) followed by 15α-allyl-3-methoxyestra-1,3,5(10)-trien-17α-ol **107** (27 mg, 26%), as an oil; δ_H (200 MHz) 0.75 (3H, s, 13β-Me), 2.85 (2H, m, 6-H_2), 3.70 (1H, d, *J* 5.3 Hz, 17β-H), 3.77 (3H, s, 3-OMe), 5.02 (2H, m $W_{½}$ 15 Hz, 15^3-H_2), 5.75-5.96 (1H, m, 15^2-H), 6.61 (1H, d, *J* 2.8 Hz, 4-H), 6.70 (1H, dd, *J* 8.5 and 2.8 Hz, 2-H) and 7.22

(1H, d, *J* 8.5 Hz, 1-H). Further elution with ethyl acetate-toluene (1:19) afforded the 17β-alcohol **103** (47 mg, 47%) identical to material prepared previously.

15β-(But-3-enyl)-3-methoxyestra-1,3,5(10)-trien-17-one 108

HMPA (7 cm^3, 43 mmol) and copper(I) iodide-dimethylsulfide complex (2.2 g, 9.1 mmol) were added to a cooled (0°C) solution of but-1-en-4-ylmagnesium bromide [prepared from 4-bromobut-1-ene (2 cm^3; 20 mmol), magnesium (500 mg, 20 mmol) and catalytic iodine] in THF (10 cm^3) and the mixture was allowed to stir for 5 min at 0°C. To the resulting solution was added a solution of 3-methoxyestra-1,3,5(10),15-tetraen-17-one **87** (500 mg, 1.8 mmol) and chlorotrimethylsilane (6 cm^3, 43 mmol) in THF (15 cm^3) over 15 min at 0°C and the mixture was allowed to stir for 1h at 0°C. Saturated aqueous ammonium chloride was added, followed by aqueous ammonia and the resulting mixture was extracted into ethyl acetate. The combined organic phase was washed [aq. NH_3 (25%), aq. HCl (1 mol dm^{-3}), water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (594 mg) which was adsorbed onto silica gel (50 g) and eluted with ethyl acetate-hexane (1:9) to give the 15β-*butenyl* 17-*ketone* **108** (474 mg, 80%), m.p. 126-128°C (from diisopropyl ether); $[\alpha]_D$ +108° (*c* 0.1) (Found: C, 81.6; H, 9.1%; M^+, 338. $C_{23}H_{30}O_2$ requires C, 81.6; H, 8.9%; *M*, 338); ν_{max}/cm^{-1} 1725 (C=O); δ_H (200 MHz) 1.02 (3H, s, 13β-Me), 3.78 (3H, s, 3-OMe), 4.95-5.10 (2H, m, 15^4-H_2), 5.70-5.92 (1H, m, 15^3-H), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.18 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 17.7 (13β-Me), 25.5 (C-11), 26.8 (C-7), 29.5 (C-6), 30.4 ($C-15^1$), 33.6 (C-12 and $C-15^2$), 33.9 (C-15), 36.0 (C-8), 42.7 (C-16), 44.5 (C-9), 47.2 (C-13), 52.8 (C-14), 55.2 (3-OMe), 111.4 (C-2), 113.9 (C-4), 115.3 ($C-15^4$), 126.0 (C-1), 132.4 (C-10), 137.7 (C-5), 138.1 ($C-15^3$), 157.7 (C-3) and 221.1 (C-17).

15β-Formylethyl-3-methoxyestra-1,3,5(10)-trien-17-one 109

Osmium tetroxide (200 mg, 0.8 mmol) was stirred with the 15β-butenyl 17-ketone **108** (200 mg, 0.6 mmol) in pyridine (3 cm^3) for 72h at 25°C. Sodium metabisulfite (2 g) in water (5 cm^3) was added and the mixture was stirred for 2h and then was extracted with chloroform. The combined organic phase was washed [aq. HCl (3 mol dm^{-3}), water], dried

($MgSO_4$) and evaporated under reduced pressure to give a foam (197 mg) which was adsorbed onto silica gel (17 g) and eluted with methanol-chloroform (1:19) to give an inseparable mixture (*ca.* 1:1, ^{1}H NMR estimate from the signals for 13β-Me) of 15β-(3*R*,4-dihydroxybutyl)-3-methoxyestra-1,3,5(10)-triene-17-one and 15β-(3*S*,4-dihydroxybutyl)-3-methoxyestra-1,3,5(10)-triene-17-one (170 mg, 76%), as a foam, *m/z* 372; ν_{max}/cm^{-1} 3615 (OH), 1725 (C=O), δ_H (200 MHz) 1.03 and 1.04 (3H, s, 13β-Me), 1.61 (2H, s, D_2O exch., 15^3- and 15^4-OH), 3.4-3.5 (1H, m, 15^3-H), 3.6-3.75 (2H, m, 15^4-H$_2$), 3.78 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H) and 7.20 (1H, d, *J* 8.5 Hz, 1-H). A portion of this mixture, (153 mg, 0.4 mmol) was dissolved in ethanol (5 cm^3) and was added to an aqueous solution of sodium periodate (0.5 mol dm^{-3}, 10 cm^3, 5 mmol) and the mixture was stirred for 16 h at 25°C. Water was added and the resulting mixture was extracted into chloroform. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give the formylethyl ketone **109** (132 mg, 95%); ν_{max}/cm^{-1} 1725 (C=O); *m/z* 340; δ_H (200 MHz) 1.03 (3H, s, 13β-Me), 3.4-3.7 (2H, m, 15^2-H$_2$), 3.76 (3H, s, 3-OMe), 6.62 (1H, d, *J* 2.7 Hz, 4-H), 6.72 (1H, dd, *J* 8.7 and 2.7 Hz, 2-H), 7.20 (1H, d, *J* 8.5 Hz, 1-H) and 9.80 (1H, s, 15^3-H).

Attempted intramolecular reductive coupling of the formylethyl ketone 109

A mixture of titanium trichloride bis(dimethoxyethane) [$TiCl_3(DME)_2$] [159] (800 mg, 2.4 mmol) and a zinc-copper couple (500 mg, 7.7 mmol) in dimethoxyethane (4 cm^3) was refluxed for 2h. The mixture was then cooled to 0°C and a solution of the formylethyl ketone **109** (130 mg, 0.4 mmol) in DME (4 cm^3) was added over a period of 10 min. The resulting solution was stirred at this temperature for 30 min, then allowed to warm to 25°C, stirred at this temperature for 18h and then refluxed for 4h. Water was added to the cooled solution and the resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (58 mg) which TLC indicated was a complex mixture. Chromatography on silica gel (5 g) with ethyl acetate-toluene (2:3) failed to elute any steroidal products.

15β-Iodomethyl-3-methoxyestra-1,3,5(10)-trien-17-one 111

To a suspension of sodium hydride (80 mg, 2 mmol) in dry DMF (4 cm^3) was added trimethylsulfoxonium iodide (400 mg, 2 mmol) in small portions over a 10 minute period. The resulting suspension was stirred for a further 30 min and then the 3-methoxyestra-1,3,5(10),15-tetraen-17-one **87** (130 mg, 0.5 mmol) in DMF (8 cm^3) was added, the mixture was stirred for 2h and then was poured into cold (0°C) hydrochloric acid (3 mol dm^{-3}, 10 cm^3). The resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give 15β,16β-methylene-3-methoxyestra-1,3,5(10)-trien-17-one **110** (130 mg, 100%), m.p. 172-174°C (from dichloromethane-methanol); $[\alpha]_D$ +14° (*c* 0.6) (lit., [168] 171-172°C; $[\alpha]_D$ +10°) (Found: C, 80.7; H, 8.3%; M^+, 296. $C_{20}H_{24}O_2$ requires C, 81.0; H, 8.2%; *M*, 296); ν_{max}/cm^{-1} 1709 (C=O); δ_H (200 MHz) 0.99 (3H, s, 13β-Me), 2.90-3.00 (2H, m, 6-H_2), 3.78 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.18 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 17.3 (13β-Me), 20.3 (C-16^1), 22.0 (C-15), 25.6 (C-11), 25.8 (C-16), 26.6 (C-7), 29.4 (C-6), 35.4 (C-12), 37.1 (C-8), 42.5 (C-13), 44.7 (C-9), 51.4 (C-14), 55.1 (3-OMe), 111.4 (C-2), 113.9 (C-4), 125.8 (C-1), 132.2 (C-10), 137.6 (C-5), 157.6 (C-3) and 216.4 (C-17).

Chlorotrimethylsilane (0.2 cm^3, 1.2 mmol) was added to a mixture of sodium iodide (200 mg, 1.3 mmol) and the 15β,16β-methylene 17-ketone **110** (130 mg, 0.4 mmol) in acetonitrile (10 cm^3) and the mixture was allowed to stir at 25°C for 1h. Water was added and the mixture was extracted with ethyl acetate. The combined organic phase was washed (water), dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue (162 mg) which was adsorbed onto silica gel (18 g) and eluted with ethyl acetate-toluene (1:9) to give the 15β-*iodomethyl* 17-*ketone* **111** (111 mg, 60%), m.p. 192-194°C (from chloroform-methanol); $[\alpha]_D$ +84° (*c* 1.3) (Found: C 56.4; H, 6.0%; M^+, 424. $C_{20}H_{25}IO_2$ requires C, 56.6; H, 5.9%; *M*, 424); ν_{max}/cm^{-1} 1731 (C=O); δ_H (200 MHz) 1.05 (3H, s, 13β-Me), 2.90-3.00 (2H, m, 6-H_2), 3.24 (1H, dd, *J* 12.8 and 9.7 Hz, 15^1-$H_{pro\text{-}R}$), 3.50 (1H, dd, *J* 12.8 and 2.9 Hz, 15^1-$H_{pro\text{-}S}$), 3.78 (3H, s, 3-OMe), 6.65 (1H, d, *J* 2.7 Hz, 4-H), 6.71 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.18 (1H, d, *J* 8.5 Hz, 1-H); δ_C (50 MHz) 8.8 (C-15^1), 18.2 (13β-Me), 25.3 (C-11), 27.1 (C-7), 29.3 (C-6), 33.8 (C-12), 35.8 (C-8), 39.2 (C-15),

43.7 (C-16), 44.4 (C-9), 47.2 (C-13), 53.4 (C-14), 55.2 (3-OMe), 111.5 (C-2), 113.9 (C-4), 125.9 (C-1), 131.8 (C-10), 137.4 (C-5), 157.8 (C-3) and 218.2 (C-17).

Attempted intramolecular Barbier reaction of the 15β-iodomethyl 17-ketone 111

A solution of tris-(dibenzoylmethido)iron(III) [$Fe(DBM)_3$] [167] (7 mg, 0.01 mmol) in THF (2 cm^3) was added to a solution of samarium(II) iodide [prepared from samarium (50 mg, 0.3 mmol) and 1,2-diiodoethane (85 mg, 0.3 mmol)] in THF (2 cm^3) and the mixture was stirred for 5 min at 25°C. To this solution was added the 15β-iodomethyl 17-ketone **111** (77 mg, 0.2 mmol) in THF (3 cm^3) and the mixture was refluxed for 2h. Saturated aqueous ammonium chloride was added and the resulting mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a residue (45 mg) which was adsorbed onto silica gel (5 g) and eluted with ethyl acetate-hexane (1:9) to give an unidentified non-steroidal product (9 mg) followed by 3-methoxy-15β-methylestra-1,3,5(10)-trien-17-one **112** (20 mg, 38%), m.p. 122-125°C (from acetone-methanol) [lit., [191] 122.5-124°C (from acetone-methanol)]; ν_{max}/cm^{-1} 1726 (C=O); δ_H (200 MHz) 1.07 (3H, s, 13β-Me), 1.16 (3H, d, *J* 7.3 Hz, 15β-Me), 2.91 (2H, m, 6-H_2), 3.79 (3H, s, 3-OMe), 6.66 (1H, d, *J* 2.7 Hz, 4-H), 6.73 (1H, dd, *J* 8.5 and 2.7 Hz, 2-H) and 7.20 (1H, d, *J* 8.5 Hz, 1-H).

3-Methoxy-14,17α-propanoestra-1,3,5(10)-trien-17β-yl Acetate 115

A solution of 3-methoxy-14,17α-propanoestra-1,3,5(10)-trien-17β-ol [34] (23 mg, 0.07 mmol) and toluene-*p*-sulfonic acid (10 mg) in THF (1 cm^3) and acetic anhydride (1 cm^3) was stirred for 18h at 25°C. Water and solid sodium hydrogen carbonate were added, and once effervescence ceased the mixture was extracted into ethyl acetate. The combined organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue (30 mg) which was chromatographed on silica gel (10 g) with ethyl acetate-toluene (1:19) as eluent to give the *product* **115** (20 mg, 78%), m.p. 143-145 C (from isopropanol); $[\alpha]_D$ +29° (*c* 0.2) (Found: C, 77.8; H 8.7%; M^+ 368. $C_{24}H_{32}O_3$ requires C, 78.2; H 8.8%; *M* 368) and ν_{max}/cm^{-1} 1723.

Crystal structure determinations

3-Methoxy-17^2*R*-phenylsulfonyl-14,17α-ethano-8α-estra-1,3,5(10),15-tetraen-17β-yl acetate 17

Crystal data

$C_{29}H_{32}O_5S$, *M* 492.61; orthorhombic, space group $P2_12_12_1$, a = 8.376(4), b = 11.979(2), c = 24.376(4) Å, V = 2445.9(12) Å^3, Z = 4, D_C = 1.338 g cm^{-3} , μ = 0.171 mm^{-1}, F(000) = 1048. A colourless crystal of dimensions 0.35 x 0.35 x 0.50 mm was used for data collection.

Data collection and processing

A single crystal of diffraction quality was mounted in a Lindemann capillary. X-ray intensity data were collected at 298K on an Enraf-Nonius CAD4 diffractometer, using graphite-monochromated Mo-Kα radiation (λ=0.7107Å) and the ω-2θ mode; 2465 reflections measured ($2 \leq 2\theta \leq 50$; $0 \leq h \leq 9$, $0 \leq k \leq 14$, $0 \leq l \leq 28$); 2465 independent reflections with $I > 2\sigma I$ (R = 0.0436). The unit cell was refined using the setting angles of 24 reflections in the θ range 16-17°. Three reference reflections were monitored periodically for intensity and orientation control. A Lorentz-polarisation correction was applied to the data.

Structure analysis and refinement

All non-hydrogen atoms were found by direct methods using SHELXS-86. [192] The structure was refined by full-matrix least-squares on F^2 using SHELXL-93. [193] The S and O atoms were treated anisotropically, as well as C19, C20, C21 and the carbon atoms in the phenyl group (C22-C27). All hydrogen atoms were placed in geometrically calculated positions and linked to a common temperature factor for chemically equivalent groups. Analysis and refinement details are : number of parameters = 230; max/min residual electron density 0.326/-0.358 e Å^{-3}; R_1 = 0.0436; wR_2 = 0.1081; Goodness-of-fit on F^2 = 1.068. The refined atom co-ordinates are given in Table 6.1.

Table 6.1: Atomic co-ordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3). U_{equiv} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	*x/a*	*y/b*	*z/c*	U_{equiv}
C(1)	14988(5)	3701(3)	11461(2)	36(1)
C(2)	15943(5)	3019(3)	11773(2)	39(1)
C(3)	15355(5)	2005(4)	11956(2)	38(1)
C(4)	13823(5)	1678(4)	11818(2)	39(1)
C(5)	12863(5)	2357(3)	11489(2)	35(1)
C(6)	11230(5)	1956(4)	11325(2)	39(1)
C(7)	10548(6)	2591(3)	10834(2)	37(1)
C(8)	10677(5)	3850(3)	10953(2)	30(1)
C(9)	12438(5)	4209(3)	10981(2)	30(1)
C(10)	13432(5)	3397(3)	11316(2)	30(1)
C(11)	13214(5)	4424(4)	10414(2)	36(1)
C(12)	12263(5)	5214(3)	10050(2)	33(1)
C(13)	10558(5)	4777(3)	9976(2)	31(1)
C(14)	9755(5)	4589(3)	10554(2)	29(1)
C(15)	8065(5)	4320(3)	10374(2)	35(1)
C(16)	7755(5)	4909(3)	9921(2)	36(1)
C(17)	9230(5)	5594(3)	9798(2)	33(1)
C(17A)	9291(5)	6533(3)	10228(1)	32(1)
C(17B)	9654(5)	5853(3)	10750(2)	30(1)
C(18)	10621(6)	3759(4)	9595(2)	39(1)
C(19)	15781(7)	452(4)	12552(2)	61(2)
C(20)	8428(6)	6685(4)	9019(2)	42(1)
C(21)	8865(7)	6997(5)	8450(2)	59(1)
C(23)	8208(6)	8376(3)	11332(2)	42(1)
C(22)	8775(5)	7414(3)	11568(2)	31(1)
C(24)	8606(7)	9389(4)	11561(2)	55(1)
C(27)	9700(7)	7455(4)	12034(2)	49(1)
C(25)	9512(7)	9438(4)	12022(2)	56(1)
C(26)	10057(7)	8485(4)	12261(2)	57(1)
S(1)	8226(1)	6104(1)	11291(1)	34(1)
O(1)	16405(4)	1392(3)	12273(1)	52(1)
O(2)	9467(4)	5953(2)	9237(1)	39(1)
O(3)	7275(5)	7031(3)	9256(1)	65(1)
O(4)	6649(3)	6225(3)	11067(1)	47(1)
O(5)	8470(5)	5279(2)	11714(1)	52(1)

3-Methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate 113

Crystal data

$C_{23}H_{30}O_3$, *M* 354.49; orthorhombic, space group $P2_12_12_1$, a = 18.669(4), b = 8.1387(6), c = 25.277(4) Å, V = 3841(1) $Å^3$, Z = 8, D_C = 1.23 g cm^{-3} , μ = 0.74 mm^{-1}, F(000) = 1536. A colourless crystal of dimensions 0.35 x 0.35 x 0.40 mm was used for data collection.

Data collection and processing

Intensity X-ray data were collected at 298K on an Enraf-Nonius CAD4 diffractometer, using graphite-monochromated Mo-Kα radiation (λ=0.7107Å) and the ω-2θ mode; 5211 reflections measured ($2 \leq 2\theta \leq 56$; $0 \leq h \leq 24$, $0 \leq k \leq 10$, $0 \leq l \leq 33$); 2437 independent reflections with $I > 2\sigma I$ (R = 0.053). The unit cell was refined using the setting angles of 24 reflections in the θ range 16-17°. Three reference reflections were monitored periodically for intensity and orientation control. A Lorentz-polarisation correction was applied to the data.

Structure analysis and refinement

All non-hydrogen atoms were found by direct methods using SHELXS-86. [192] The structure was refined by full-matrix least-squares using SHELX76. [194] All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed in geometrically calculated positions and linked to a common temperature factor. Analysis and refinement details are : number of parameters = 489; max/min residual electron density 0.21/-0.25 e $Å^{-3}$; R = 0.053; Rw = 0.045. There are two crystallographically independent molecules in the asymmetric unit, distinguished by the labels A and B. The refined atom co-ordinates are given in Table 6.2.

Table 6.2: Atomic co-ordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3). U_{equiv} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	*x/a*	*y/b*	*z/c*	U_{equiv}
C1A	2336(3)	10691(7)	3019(2)	57(2)
C2A	2325(3)	11365(7)	3513(2)	60(2)
C3A	2175(3)	10388(7)	3951(2)	49(2)
C4A	2001(3)	8756(7)	3880(2)	41(2)
C5A	1993(2)	8087(6)	3373(2)	39(2)
C6A	1794(3)	6287(6)	3318(2)	45(2)
C7A	1740(3)	5661(7)	2755(2)	47(2)
C8A	2316(3)	6430(6)	2408(2)	37(2)
C9A	2193(3)	8299(6)	2379(2)	41(2)
C10A	2173(3)	9035(6)	2933(2)	40(2)
C11A	2733(3)	9147(6)	2006(2)	54(2)
C12A	2786(3)	8338(6)	1456(2)	47(2)
C13A	2944(3)	6510(6)	1509(2)	40(2)
C14A	2376(3)	5679(6)	1863(2)	40(2)
C15A	2606(3)	3836(6)	1841(2)	51(2)
C16A	2881(3)	3642(7)	1261(2)	58(2)
C17A	2777(3)	5388(6)	1034(2)	42(2)
C171	1979(3)	5665(7)	938(2)	53(2)
C172	1685(3)	5787(7)	1514(2)	50(2)
C18A	3728(3)	6287(8)	1690(2)	52(2)
O19A	2205(2)	11159(5)	4436(1)	67(1)
C20A	2105(4)	10181(8)	4894(2)	68(3)
O21A	3233(2)	5808(4)	590(1)	49(1)
C22A	3198(4)	4922(8)	146(3)	59(3)
O23A	2801(3)	3785(6)	78(2)	86(2)
C24A	3714(3)	5549(9)	-261(2)	67(3)

Table 6.2: (cont.) Atomic co-ordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3). U_{equiv} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	*x/a*	*y/b*	*z/c*	U_{equiv}
C1B	-126(3)	3684(7)	1262(2)	48(2)
C2B	-25(3)	3211(7)	1788(2)	54(2)
C3B	416(3)	1904(8)	1896(2)	64(3)
C4B	715(3)	1037(8)	1487(3)	68(3)
C5B	607(3)	1483(8)	966(2)	60(2)
C6B	977(4)	472(8)	544(2)	81(3)
C7B	749(3)	921(7)	-17(2)	64(3)
C8B	706(3)	2769(6)	-81(2)	47(2)
C9B	103(3)	3450(6)	276(2)	43(2)
C10B	201(3)	2869(7)	842(2)	45(2)
C11B	47(3)	5339(7)	231(2)	49(2)
C12B	-12(3)	5929(7)	-346(2)	51(2)
C13B	612(3)	5284(6)	-673(2)	41(2)
C14B	640(3)	3380(7)	-643(2)	49(2)
C15B	1267(3)	2972(8)	-1016(2)	63(3)
C16B	1177(3)	4284(8)	-1471(2)	65(2)
C17B	526(3)	5285(8)	-1284(2)	50(2)
C173	-141(3)	4233(8)	-1379(2)	67(3)
C174	-55(3)	2882(8)	-948(2)	63(2)
C18B	1301(3)	6213(8)	-512(9)	57(2)
O19B	576(3)	1382(6)	2398(2)	90(2)
C20B	347(4)	2355(9)	2829(3)	85(3)
O21B	491(2)	6961(5)	-1465(1)	60(2)
C22B	579(3)	7329(9)	-1981(3)	63(3)
O23B	610(3)	6324(7)	-2318(2)	100(2)
C24B	620(4)	9146(8)	-2051(2)	75(3)

3-Methoxy-14,17α-propanoestra-1,3,5(10)-trien-17β-yl acetate 115

Crystal data

$C_{24}H_{32}O_3$, *M* 368.52; orthorhombic, space group $P2_1$, *a* = 7.303(2), *b* = 27.726(4), *c* = 10.498(3) Å, β = 107.43(2)°, V = 2028.1(9) $Å^3$, Z = 4, D_C = 1.21 g cm^{-3} , μ = 0.73 mm^{-1}, F(000) = 800. A colourless crystal of dimensions 0.25 x 0.13 x 0.13 mm was used for data collection.

Data collection and processing

Intensity X-ray data were collected at 298K on an Enraf-Nonius CAD4 diffractometer, using graphite-monochromated Mo-Kα radiation (λ=0.7107Å) and the ω-2θ mode; 4051 reflections measured ($2 \leq 2\theta \leq 50$; $-8 \leq h \leq 8$, $0 \leq k \leq 33$, $0 \leq l \leq 12$); 1336 independent reflections with $I > 2\sigma I$ (*R* = 0.071). The unit cell was refined using the setting angles of 24 reflections in the θ range 16-17°. Three reference reflections were monitored periodically for intensity and orientation control. A Lorentz-polarisation correction was applied to the data.

Structure analysis and refinement

All non-hydrogen atoms were found by direct methods using SHELXS-86. [192] The structure was refined by blocked full-matrix least-squares using SHELX76. [194] All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed in geometrically calculated positions and linked to a common temperature factor. Analysis and refinement details are : number of parameters = 254; max/min residual electron density 0.29/-0.26 e $Å^{-3}$; *R* = 0.071; *Rw* = 0.056. There are two crystallographically independent molecules in the asymmetric unit, distinguished by the labels A and B. The refined atom co-ordinates are given in Table 6.3.

Table 6.3: Atomic co-ordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3). U_{equiv} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	*x/a*	*y/b*	*z/c*	U_{equiv}
C1A	3940(22)	8866(5)	8862(14)	60(7)
C2A	3658(21)	9367(6)	8634(14)	72(8)
C3A	1751(27)	9535(7)	8352(16)	78(9)
C4A	263(22)	9210(6)	8294(13)	59(7)
C5A	638(20)	8717(5)	8510(11)	44(6)
C6A	-1092(18)	8387(6)	8426(14)	64(7)
C7A	-631(17)	7869(6)	8364(13)	62(7)
C8A	1321(17)	7734(4)	9371(12)	37(6)
C9A	2933(17)	7997(5)	8966(12)	42(7)
C10A	2513(21)	8528(5)	8772(12)	44(7)
C11A	4894(15)	7887(4)	9926(14)	44(6)
C12A	5271(17)	7348(5)	10269(13)	64(7)
C13A	3626(16)	7111(5)	10666(12)	40(6)
C14A	1685(16)	7207(5)	9609(12)	46(6)
C15A	293(17)	6910(5)	10113(14)	57(6)
C16A	1559(17)	6485(4)	10937(12)	51(7)
C17A	3576(22)	6563(5)	10889(15)	56(7)
C171	3774(20)	6299(6)	9664(16)	83(8)
C172	2207(25)	6401(6)	8418(16)	87(9)
C173	1729(19)	6937(5)	8259(13)	73(8)
C18A	3727(16)	7355(4)	12039(12)	50(5)
O19A	5188(16)	6434(0)	12000(12)	77(6)
C20A	5450(37)	6055(8)	12555(12)	116(14)
O21A	4139(19)	5702(5)	12185(15)	128(8)
C22A	7197(23)	5951(6)	13607(19)	124(11)
O23A	1534(17)	9998(4)	8231(11)	91(7)
C24A	-366(27)	10202(7)	8054(20)	110(11)

Table 6.3: (cont.) Atomic co-ordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3). U_{equiv} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	*x/a*	*y/b*	*z/c*	U_{equiv}
C1B	4711(18)	7473(6)	5935(12)	54(7)
C2B	5238(19)	7012(5)	6091(14)	64(7)
C3B	3873(24)	6671(6)	5529(14)	63(8)
C4B	1979(22)	6790(6)	4900(13)	61(8)
C5B	1492(17)	7270(6)	4781(13)	51(7)
C6B	-559(19)	7386(6)	3990(14)	66(8)
C7B	-1093(17)	7905(5)	4010(15)	72(7)
C8B	519(17)	8232(5)	3823(12)	44(6)
C9B	2252(17)	8165(4)	5058(12)	37(6)
C10B	2812(19)	7652(6)	5292(13)	51(7)
C11B	3963(17)	8497(5)	5130(12)	57(6)
C12B	3402(18)	9025(5)	4684(13)	61(7)
C13B	1752(16)	9060(5)	3429(12)	40(6)
C14B	15(18)	8756(5)	3525(11)	41(6)
C15B	-1525(17)	8868(5)	2207(12)	54(6)
C16B	-998(16)	9379(5)	1791(12)	46(6)
C17B	768(19)	9519(5)	2918(13)	48(6)
C174	241(21)	9819(5)	4080(13)	70(7)
C175	-1257(22)	9514(6)	4451(15)	88(9)
C176	-732(18)	8994(5)	4661(13)	58(6)
C18B	2487(18)	8833(5)	2293(13)	68(8)
O19B	2203(13)	9826(4)	2517(9)	64(4)
C20B	1669(30)	10211(5)	1787(20)	77(10)
O21B	50(17)	10364(4)	1406(12)	105(7)
C22B	3283(26)	10463(6)	1486(18)	112(11)
O23B	4507(14)	6197(4)	5773(9)	79(5)
C24B	3184(22)	5832(5)	5220(15)	83(8)

Analysis

The crystal structure of the 14α,17α-ethano compound **113** indicated two crystallographically independent molecules in the unit cell. The major differences between these two molecules lie in the flexible ring B region, as well as in the conformation of the protecting groups. This is clearly indicated in Figure 6.1, where the two molecules have been superimposed. A complete summary of the observed bond lengths, bond angles and endocyclic torsion angles is contained in Figure 6.2 and Table 6.4. No abnormal bond lengths, angles or torsion angles were observed in the determination.

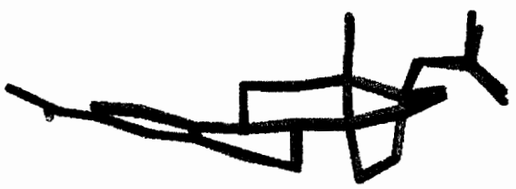
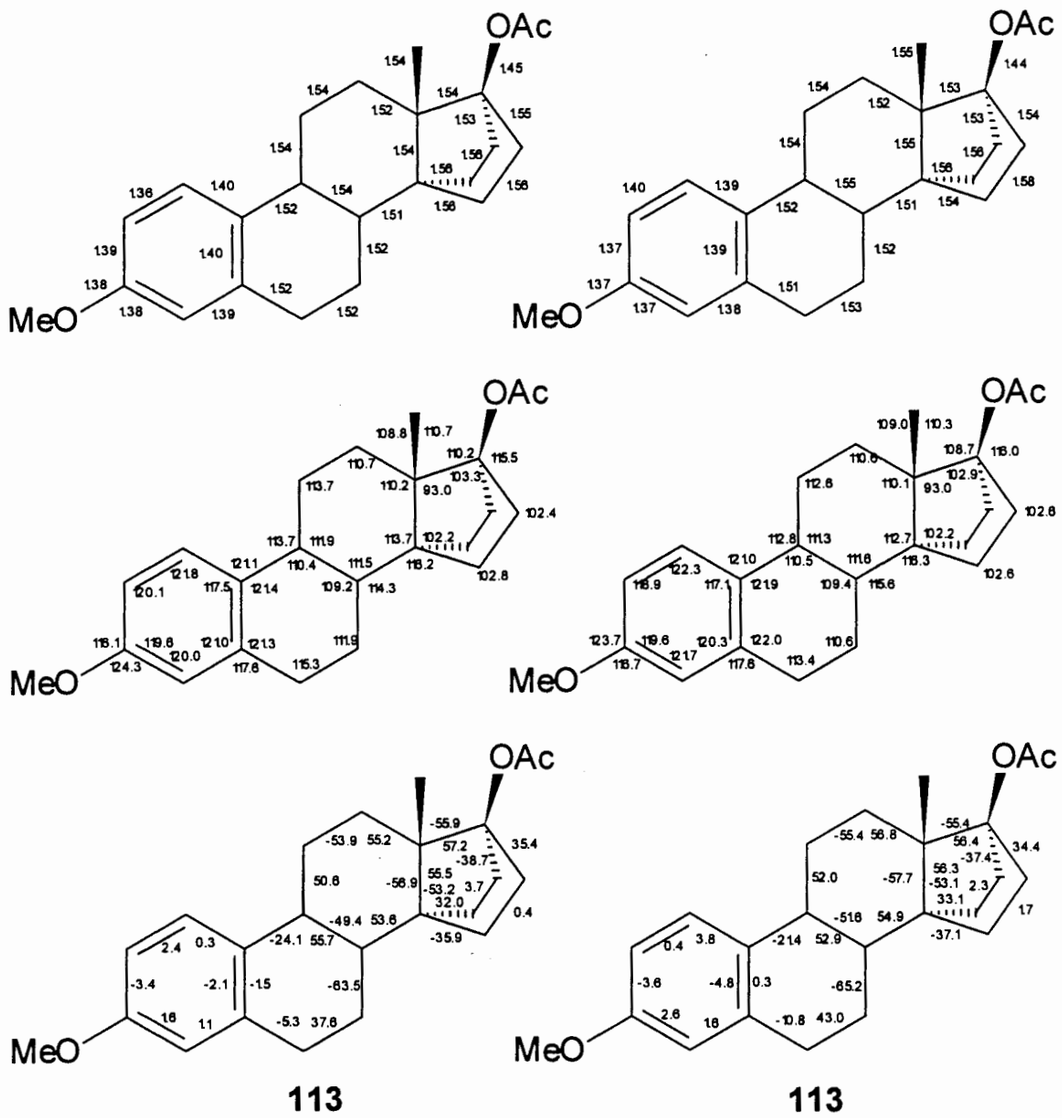


Figure 6.1: Superimposition of the two observed structures of 3-methoxy-14,17α-ethanoestra-1,3,5(10)-trien-17β-yl acetate **113**. Conformation A is displayed in green and conformation B in purple.



113 **113**

Figure 6.2: Bond distances (Å), bond angles (°) and endocyclic torsion angles (°) for the two crystallographically observed forms of 14α,17α-ethano compound **113**. A torsion angle α-β-γ-δ is positive if, when viewed down the β-γ bond, the α-β bond will eclipse the γ-δ bond when rotated less then 180° in a clockwise direction.

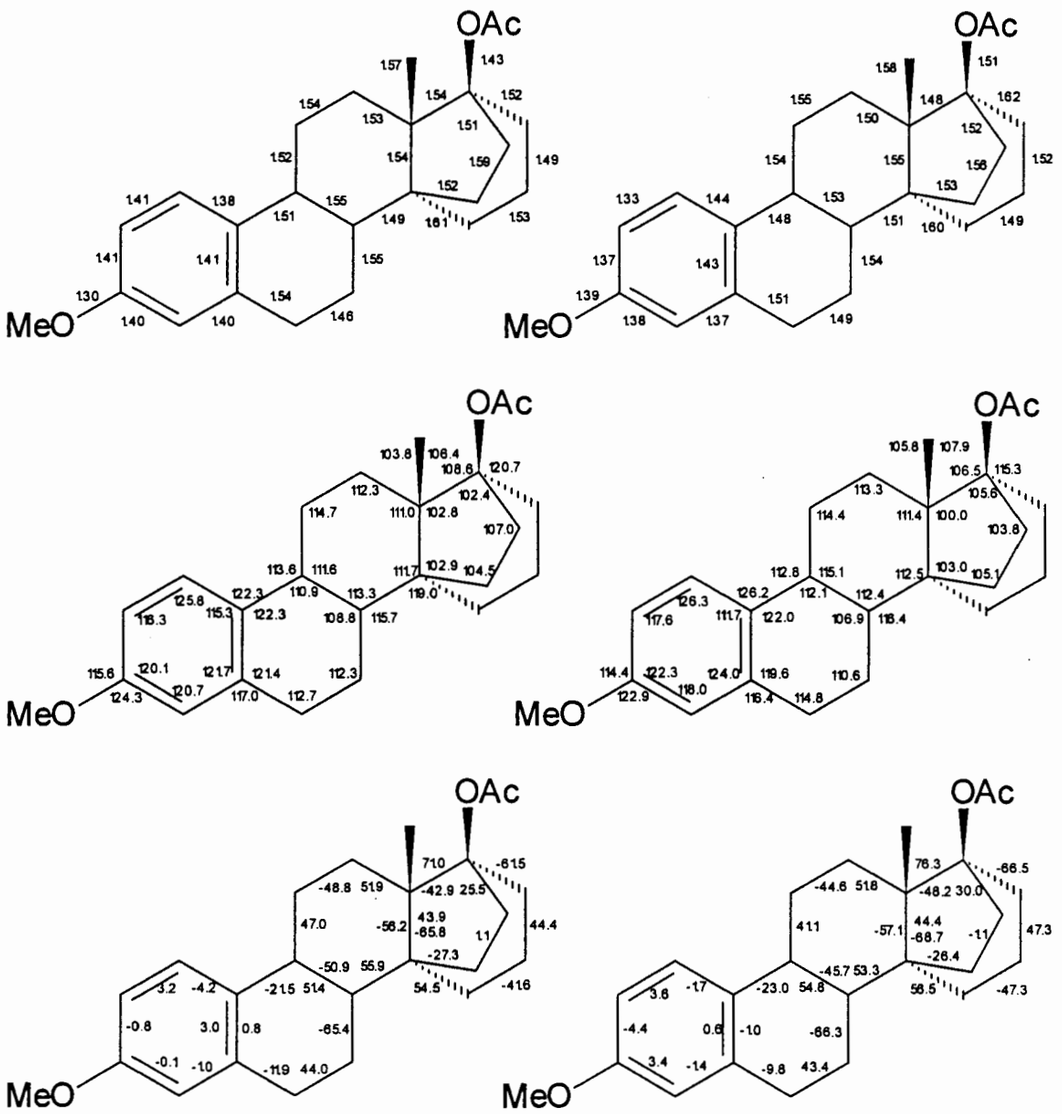
A similar pattern was observed in the case of the 14α,17α-propano compound **115**, the two crystallographically independent conformations once again mainly differed in the conformation of ring B. Interestingly, in this case, unlike as was observed for the 14α,17α-ethano compound **113** the protecting groups adopted very similar conformations.

The two conformations have been superimposed in Figure 6.3. The observed bond lengths, bond angles and torsion angles are summarised in Figure 6.4 and Table 6.4, some slightly long bonds (1.6 Å for C-C single bonds) were observed.

Figure 6.3: Superimposition of the two observed structures of 3-methoxy-14,17α-propanoestra-1,3,5(10)-trien-17β-yl acetate **115**. Conformation A is displayed in green and conformation B in purple.

Table 6.4: Additional bond angles observed in the X-ray crystal structures of the 14,17-bridged estradiol analogues **113**, **115** and **117**.

	Compound							
Angle	**60**	**60**	**115**	**115**	**117**	**117**	**117**	**117**
8-14-$17^{2/3}$	115.5	116.5	110.8	111.1	108.9	110.3	111.1	110.5
13-14-$17^{2/3}$	102.4	101.9	107.3	107.1	108.9	108.7	108.1	108.7
13-17-17^{1}	103.5	103.9	109.5	111.6	111.5	111.5	111.2	111.1
14-$17^{2/3}$-$17^{1/2}$	103.6	104.4	114.8	114.8	111.0	112.4	113.2	112.8
15-14-$17^{2/3}$	105.1	105.9	104.3	105.6	108.8	109.4	108.7	109.1
16-17-17^{1}	108.5	107.4	107.5	112.4	111.4	110.1	109.8	109.9
17-17^{1}-17^{2}	101.7	101.6	114.2	105.0	109.9	111.1	111.3	112.4
17^{1}-17-O	114.5	116.4	107.7	105.3	109.7	105.7	110.3	106.1
17^{1}-17^{2}-17^{3}	--	--	111.9	113.7	114.1	113.8	113.2	113.1



115 **115**

Figure 6.4: Bond distances (Å), bond angles (°) and endocyclic torsion angles (°) for the two crystallographically observed forms of 14α,17α-propano compound **115**. A torsion angle α-β-γ-δ is positive if, when viewed down the β-γ bond, the α-β bond will eclipse the γ-δ bond when rotated less then 180° in a clockwise direction.

Four crystallographically independent conformations were observed in the unit cell of the 14β,17β-propano compound **117**. [37] These structures differed in the conformation of ring B, and in the orientation of the 3-methoxy group. This deviation is apparent from the

superimpositions of the various observed conformations depicted in Figure 6.5. The bond lengths, bond angles and torsion angles are summarised in Figure 6.6 and Table 6.4.

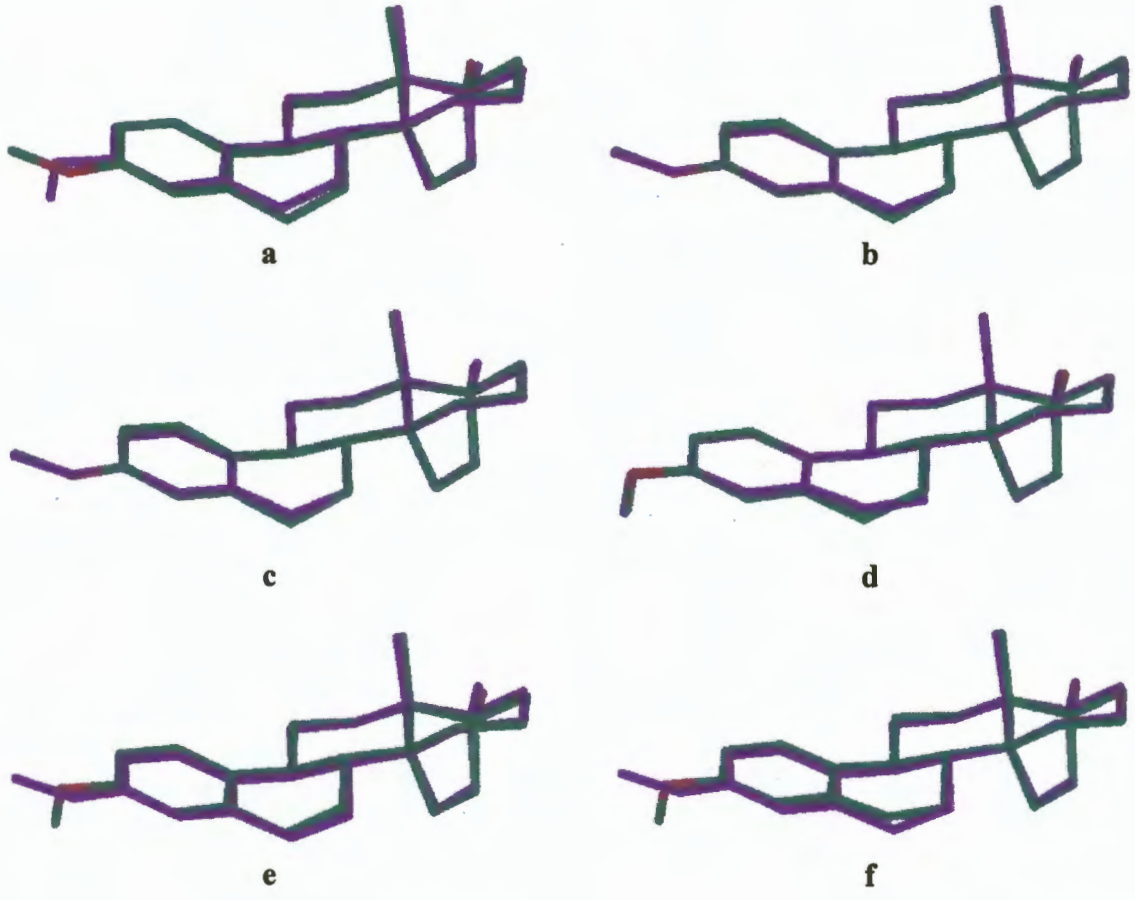


Figure 6.5: Superimposition of the four crystallographically observed conformations of 3-methoxy-14,17β-propano-14β-estra-1,3,5(10)-trien-17β-ol **117**. (**a**) A and B, (**b**) A and C, (**c**) A and D, (**d**) B and C, (**e**) B and D and (**f**) C and D. In all cases the former conformer is displayed in green and the latter in purple.

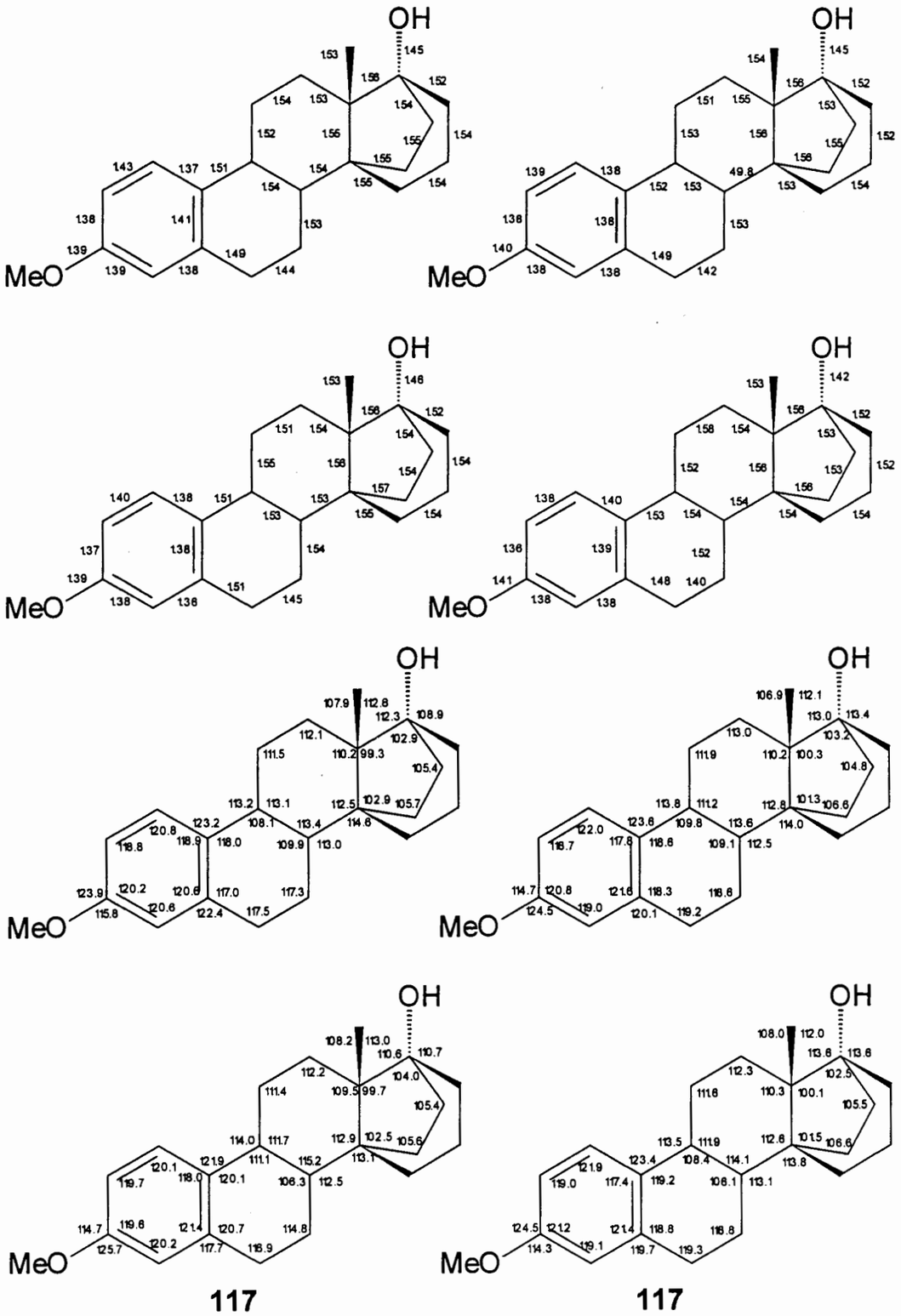


Figure 6.4: (see following page)

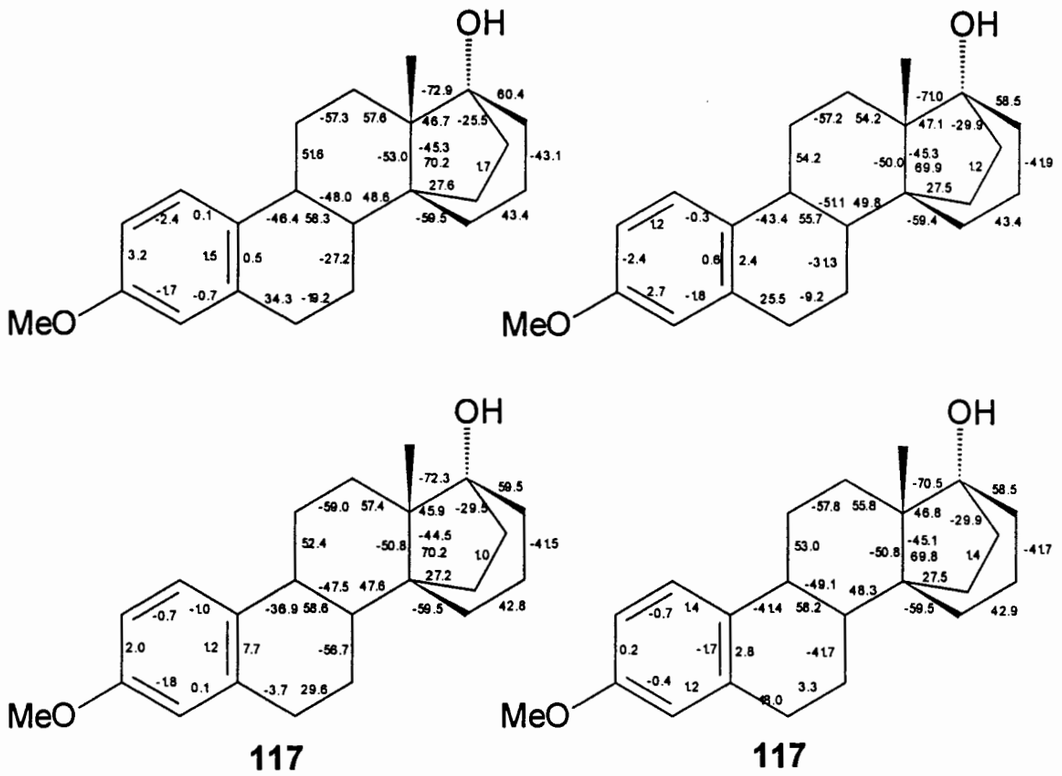


Figure 6.4: Bond distances (Å), bond angles (°) and endocyclic torsion angles (°) for the two crystallographically observed forms of 14β,17β-propano compound **117**. A torsion angle α-β-γ-δ is positive if, when viewed down the β-γ bond, the α-β bond will eclipse the γ-δ bond when rotated less then 180° in a clockwise direction.

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Appendix 1

Binding Affinity Determination

The affinities of the estradiol analogues described in this thesis were determined by the method of competitive protein binding. [24] In this technique, radioactively labelled reference hormone and the test compound are incubated with the receptor. As the test material competes for receptor site occupancy, the amount of reference material bound by the protein decreases. This competition depends on the concentration of the test material and upon it's binding affinity towards the receptor. The affinity is measured in terms of a 'competition factor' (CF), defined as the ratio of the concentration of the test sample (c_{test}) and that of the reference (c_{ref}) required for 50% competition:

$$CF = (c_{test}/c_{ref}) \text{ at } 50\% \text{ competition.}$$

In this case, estradiol was taken as the reference material, and thus has a CF of 1. A binding assay of $CF \leq 1$ indicates that the hormone analogue is biologically active, and is able to compete successfully with estradiol for receptor site occupancy. A compound with a CF of much greater than unity is considered inactive.

Appendix 2

Puckering Parameters

For a six-membered ring, three parameters of pucker in the form of polar coordinates (Q, θ, ϕ) are obtained from the calculation (as described by Cremer and Pople). [178] These coordinates map out the conformation of the ring upon the surface of a sphere, radius Q, and with poles at θ = 0, 180°. [179] Figure A2.1 depicts the surface of this sphere in a two-dimensional polar projection. [179]

In the case of a 'perfect' chair conformation, Q = 0.63Å (assuming all bonds are 1.54Å), and both θ and ϕ are 0°. As the ring distorts away from ideality, all of these parameters change. As can be seen from Figure A2.1, while θ remains at or near 0°C, any deviations of ϕ have little effect on the conformation of the ring, however, as θ increases, changes in ϕ have a greater effect on the ring conformation. Thus, the puckering parameters provide an excellent method of determining the conformation of a six-membered ring.

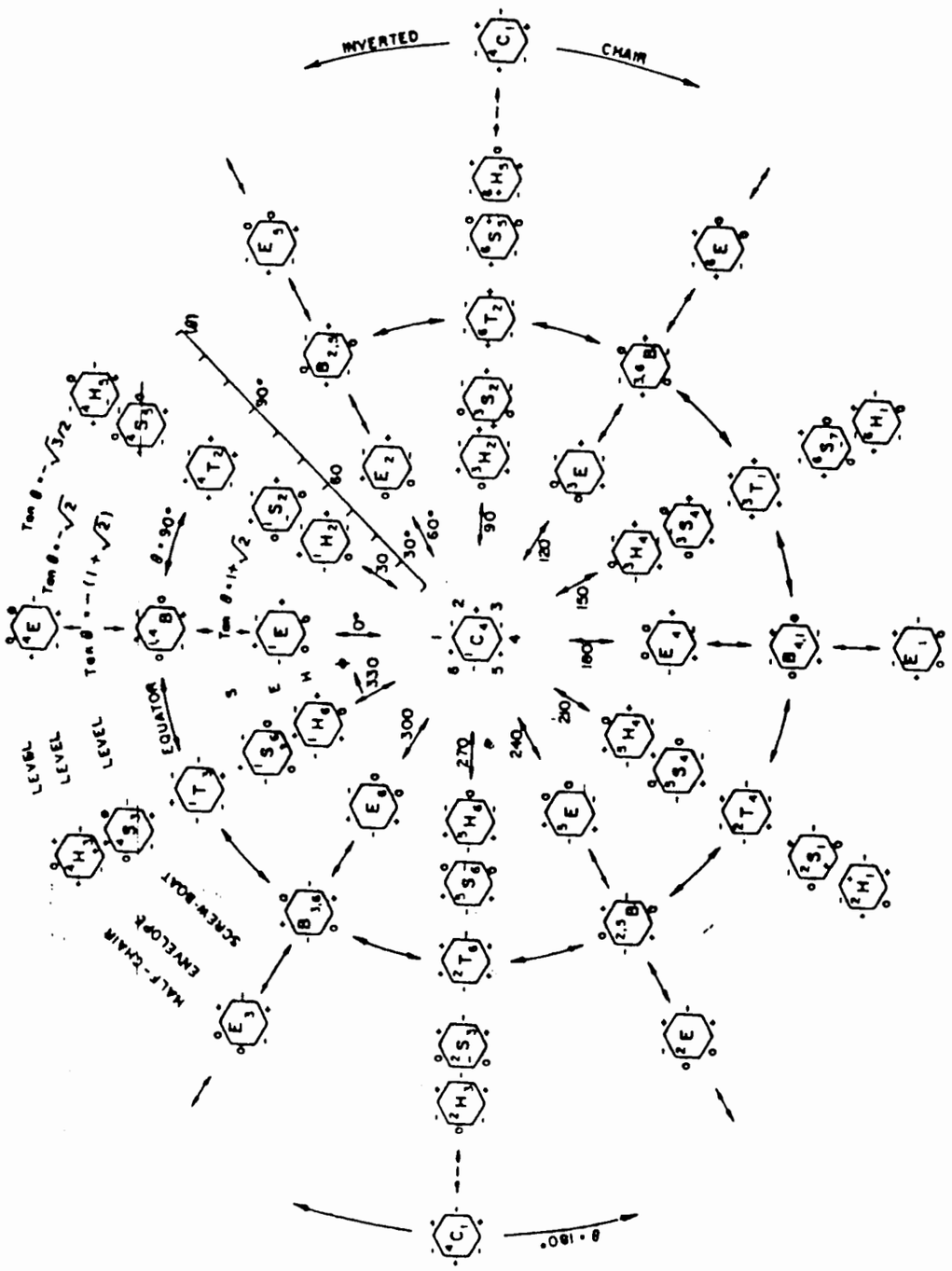


Figure A2.1: Two dimensional polar projection of a spherical surface to distinguish between the canonical conformations (reproduced from ref 179)

Appendix 3

List of Abbreviations Used

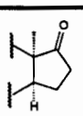
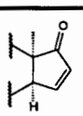
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
^{13}C NMR	Carbon-13 nuclear magnetic resonance spectroscopy
AIBN	α,α'-Azobis(isobutyronitrile)
CAN	Cerium(IV) ammonium nitrate
COSY	^{1}H-^{1}H Correlation spectroscopy
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAH	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)-pyridine
DMD	Dimethyldioxirane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
FMO	Frontier molecular orbital
HETCOR	^{1}H-^{13}C Correlation spectroscopy
HMPA	Hexamethylphosphoramide
IPA	Isopropenyl acetate
IR	Infrared
LAH	Lithium aluminium hydride
NOE	Nuclear Overhauser effect
PVS	Phenyl vinyl sulfone
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
m-cpba	*meta*-Chloroperbenzoic acid

Appendix 4

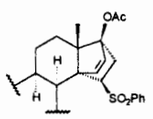
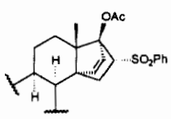
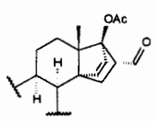
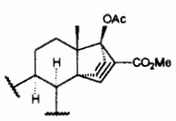
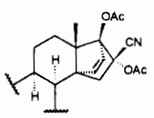
Tables of ^{13}C NMR Data

Tables of ^{13}C NMR data for selected compounds are presented. All assignments were made by a combination of 2D techniques and by analogy with previously reported values for related compounds. [66, 195] (All δ values are in ppm relative to TMS)

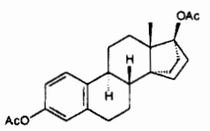
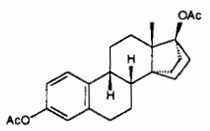
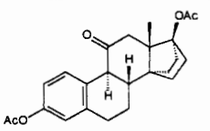
13α-Series (Section 2.1)

Carbon		
	3	**4**
1	126.8	128.0
2	111.7	112.3
3	157.5	157.4
4	113.5	113.3
5	138.0	137.2
6	30.3	29.9
7	28.3	28.2
8	41.5	41.2
9	41.4	38.4
10	131.9	132.8
11	28.2	27.0
12	32.0	29.2
13	50.1	46.5
14	49.3	56.7
15	21.0	164.0
16	33.4	131.3
17	210.0	214.2
13α-Me	25.1	24.2
3-OMe	55.1	55.2

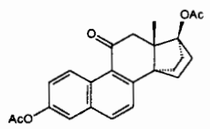
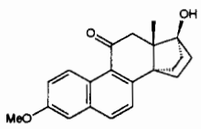
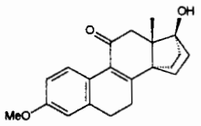
8α-series (Section 2.2)

Carbon					
	17	**18**	**31**	**33**	**37**
1	130.4	130.4	130.4	130.4	130.2
2	112.4	112.3	112.3	112.3	112.3
3	157.6	157.6	157.6	157.6	157.6
4	113.2	113.2	113.2	113.3	113.1
5	137.6	136.9	137.1	136.9	136.8
6	31.3	30.5	30.6	30.8	30.4
7	27.2	20.1	20.1	21.6	19.8
8	34.6	37.8	38.0	36.1	37.5
9	35.4	38.2	38.6	37.4	37.8
10	132.7	133.4	133.5	133.2	132.9
11	22.6	28.2	28.1	27.4	27.7
12	28.1	29.2	30.9	30.4	30.2
13	60.3	54.4	59.3	87.4	59.7
14	61.1	61.2	54.4	64.8	54.8
15	132.5	28.9	28.3	152.8	42.3
16	135.5	67.2	55.2	146.8	79.0
17	92.4	95.1	95.5	98.7	97.7
13β-Me	16.9	16.5	16.4	18.6	17.7
3-OMe	55.2	55.2	55.2	55.2	55.1
17^1	31.1	129.2	129.8	140.0	130.6
17^2	66.3	136.3	140.2	143.5	139.5
17β-OAc	21.3 and 170.4	20.9 and 168.9	21.3 and 171.2	21.4 and 170.7	21.3 and 169.2
misc.	128.1, 129.2, 133.3 and 141.3 (17^1-$PhSO_2$)	128.5, 129.1, 133.3 and 140.9 (16α-$PhSO_2$)	201.9 (16α-CHO)	51.3 and 164.7 (16-CO_2Me)	20.9 and 169.0 (16α-OAc) 117.1 (16β-CN)

9β-Series (Section 2.3)

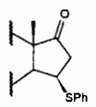
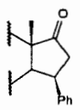
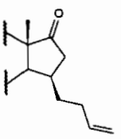
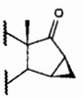
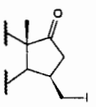
Carbon			
	61	**67**	**69**
1	126.6	124.5	131.6
2	118.6	118.8	118.6
3	148.4	148.1	148.9
4	121.5	120.3	121.6
5	138.6	141.2	138.4
6	27.7	28.4	30.1
7	23.6	23.2	24.3
8	37.9	35.3	42.5
9	40.0	34.3	50.1
10	138.2	139.3	129.2
11	26.0	21.8	209.2
12	27.2	24.5	47.1
13	48.2	48.7	54.3
14	45.1	45.2	45.4
15	32.8	33.8	31.8
16	32.0	31.8	32.2
17	89.6	89.8	88.1
17^1	29.9	29.1	29.5
17^2	29.2	28.8	27.7
3-OC(O)CH$_3$	21.1	21.2	21.1
17β-OC(O)CH$_3$	21.6	21.6	21.4
3-OC(O)CH$_3$	171.0	170.9	170.9
17β-OC(O)CH$_3$	169.9	169.7	169.6
13β-Me	14.0	14.2	14.6

Ring B unsaturated 14α,17α-ethano derivatives (Section 2.3)

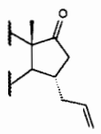
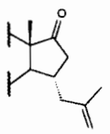
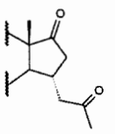
Carbon			
	80	**81**	**82**
1	128.4	128.2	128.3
2	123.8	121.0	111.0
3	148.2	157.2	157.3
4	118.9	106.6	113.3
5	133.6	134.4	137.6
6	134.5	133.6	37.4
7	124.7	124.1	25.6
8	148.2	146.5	167.0
9	125.1	125.2	156.1
10	129.5	126.9	124.0
11	200.0	200.7	200.3
12	45.6	45.2	44.0
13	46.0	49.9	48.8
14	51.0	47.9	49.9
15	32.3 *	35.8 *	34.1 *
16	39.9 *	39.3 *	35.5 *
17	88.8	83.9	83.6
17^1	31.7 *	34.6 *	29.7 *
17^2	31.2 *	31.3 *	28.0 *
misc.	21.2 and 170.7 3-OC(O)CH_3 21.4 and 169.4 17β-OC(O)CH_3	55.2 3-OMe	55.3 3-OMe

* Data are interchangeable

15β 17-Oxo series (Chapter 3)

Carbon					
	88	**98**	**108**	**110**	**111**
1	126.7	126.1	126.0	125.8	125.9
2	111.5	111.5	111.4	111.4	111.5
3	157.7	157.7	157.7	157.6	157.8
4	113.9	113.8	113.9	113.9	113.9
5	136.8	137.7	137.7	137.6	137.4
6	29.4	29.4	29.5	29.4	29.3
7	26.6	27.7	26.8	26.6	27.1
8	36.5	37.1	36.0	37.1	35.8
9	44.4	44.9	44.5	44.7	44.4
10	131.9	132.3	132.4	132.2	131.8
11	25.5	25.6	25.5	25.6	25.3
12	33.1	34.2	33.6	35.4	33.8
13	47.8	47.3	47.2	42.5	47.2
14	53.7	55.0	52.8	51.4	53.4
15	43.7	38.6	33.9	22.0	39.2
16	46.6	45.0	42.7	25.8	43.7
17	218.5	221.0	221.1	216.4	218.2
13β-Me	17.0	17.6	17.7	17.3	18.2
3-OMe	55.2	55.2	55.2	55.1	55.2
misc.	126.1, 129.2, 130.3 and 137.8 (15β-SPh)	126.0, 128.3, 128.4 and 142.8 (15β-Ph)	30.4, 33.6 (C-15[1] and C-15[2]) 138.1 (C-15[3]) 115.3 (C-15[4])	20.3 (C-16[1])	8.8 (C-15[1])

15α 17-Oxo series (Chapter 3)

Carbon			
	93	**95**	**99**
1	126.8	126.8	126.7
2	111.8	111.8	111.8
3	157.6	157.6	157.6
4	113.6	113.5	113.5
5	137.3	137.3	137.0
6	30.0	30.0	29.8
7	27.9	27.9	27.8
8	39.7	39.7	39.5
9	44.2	44.3	44.1
10	131.8	131.8	131.5
11	26.5	26.6	26.5
12	31.6	31.6	31.5
13	50.4	50.5	49.8
14	54.1	55.4	54.1
15	35.5	33.7	50.9*
16	42.6	45.5	43.9
17	219.5	219.7	219.0
13β-Me	15.7	15.8	15.5
3-OMe	55.2	55.2	55.2
misc.	40.4 (C-15^1)	22.5 (C-15^2-Me)	31.0* (C-15^1)
	136.3 (C-15^2)	42.8 (C-15^1)	207.2 (C-15^2)
	116.6 (C-15^3)	144.1 (C-15^2)	30.4 (C-15^3)
		111.6 (C-15^3)	

* Data are interchangeable

Appendix 5

X-Ray Crystal Structure of Estradiol

For comparison purposes, the relevant details of the X-ray crystal structure of estradiol [184] have been summarised in the following figure.

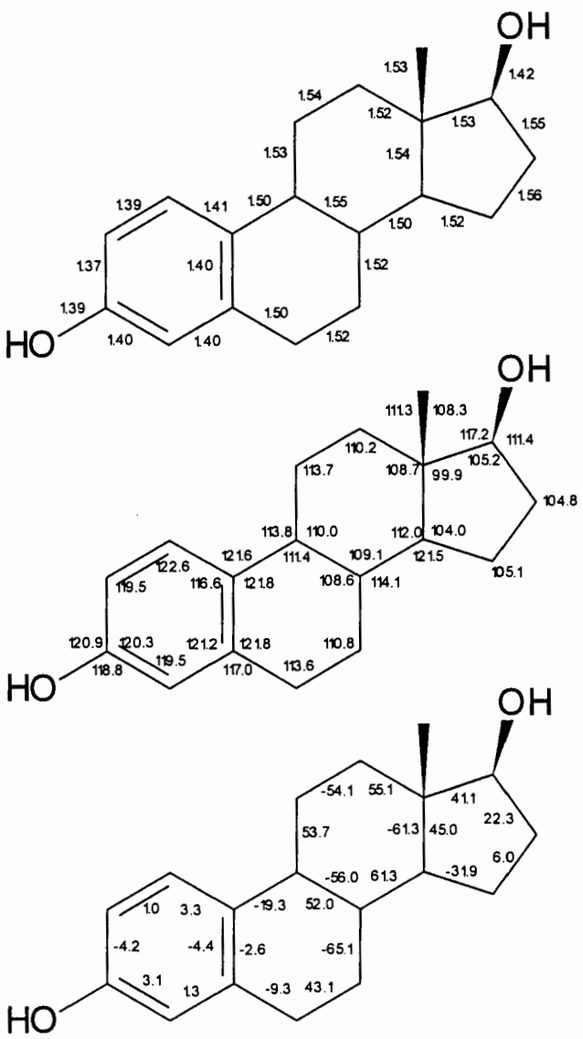


Figure A5.1: Bond distances (Å), bond angles (°) and endocyclic torsion angles (°) for the two crystallographically observed forms of estradiol. A torsion angle α-β-γ-δ is positive if, when viewed down the β-γ bond, the α-β bond will eclipse the γ-δ bond when rotated less then 180° in a clockwise direction.